

# **ORTHO SUBSTITUTED CHIRAL PHOSPHINES AND PHOSPHINITES AND THEIR USE IN ASYMMETRIC CATALYTIC REACTIONS**

## **BACKGROUND OF THE INVENTION**

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This application claims priority from U.S. Provisional Application Serial No. 60/249,537, filed November 17, 2000, and U.S. Provisional Application Serial No. 60/301221, filed June 27, 2001.

### 10    **1.    FIELD OF THE INVENTION**

The present invention relates to novel chiral ligands derived from 3,3'-substituted biaryl phosphines and phosphinites. More particularly, the present invention relates to transition metal complexes of these chiral phosphine ligands.

15    The transition metal complexes are useful as catalysts in asymmetric reactions, such as, hydrogenation, hydride transfer, allylic alkylation, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, olefin metathesis, hydrocarboxylation, isomerization, cyclopropanation, Diels-Alder reaction, Heck reaction, isomerization, Aldol reaction, Michael addition, epoxidation, kinetic

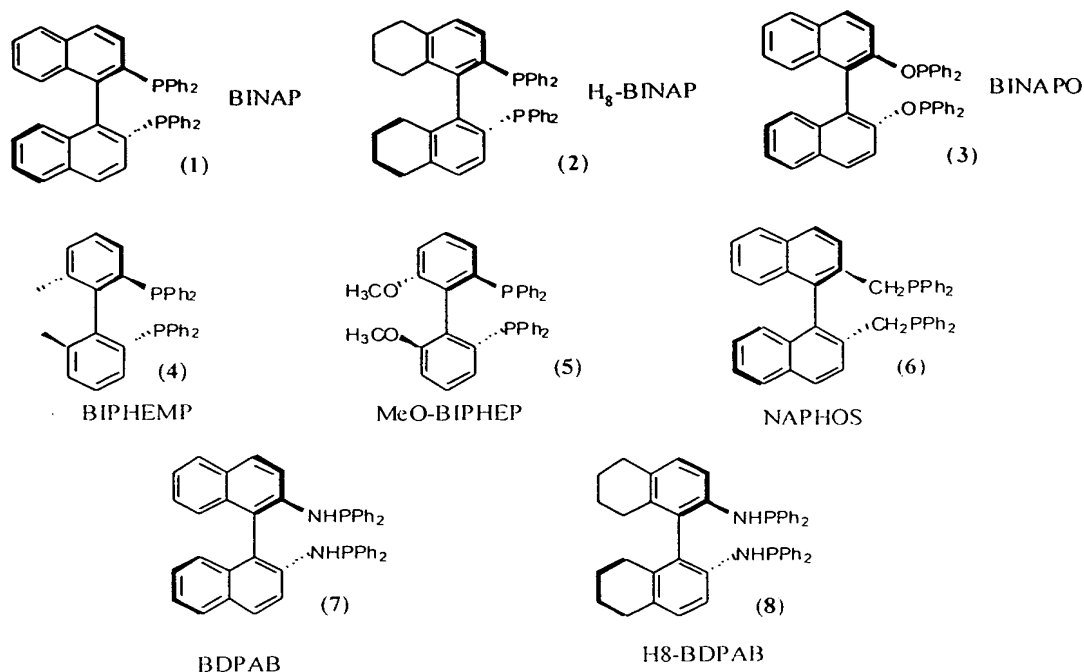
20    resolution and [m+n] cycloaddition.

### **2.    DESCRIPTION OF THE PRIOR ART**

Discovery of new chiral ligands is crucial in developing highly

25    enantioselective transition metal-catalyzed reactions. Many chiral ligands have been made for applications in asymmetric catalysis, however, relatively few of these chiral ligands are commonly used in industry for the synthesis of chiral molecules.

30    Several chiral ligands having a biaryl backbone are known in the prior art. These are summarized below:

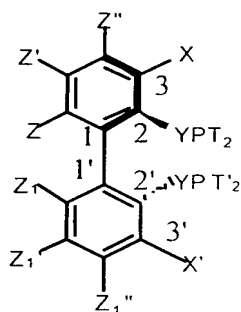


Among these ligands, BINAP (1) is one of the most frequently used chiral ligands. The axially dissymmetric, fully aromatic BINAP has demonstrated to be highly effective for many asymmetric reactions (Noyori, R. et al. *Acc. Chem. Res.* **1990**, 23, 345, Ohkuma, T. et al. *J. Am. Chem. Soc.* **1998**, 120, 13529). Recent results show that partially hydrogenated BINAP with a larger bite angle, H<sub>8</sub>-BINAP (2), is a better ligand for certain asymmetric reactions due to restriction of conformational flexibility (Zhang X. et al. *Synlett* 1994, 501). Chiral BINAPO (3) was made and it was not effective due to the conformational flexibility (Grubbs, R. et al. *Tetrahedron Lett.* **1977**, 1879). Other axially dissymmetric ligands such as BIPHEMP (4) and MeO-BIPHEP (5) were developed and used for a number of asymmetric reactions (Schmid, R. et al. *Pure & Appl. Chem.* **1996**, 68, 131; Schmide, R. et al. *Helv. Chim. Acta*, 1988, 71, 897). However, the present inventor is not aware of any examples of related 3,3' substituted chiral biaryl phosphines, the subject of the present invention, being disclosed in the prior art (Broger, E. A. et al., WO 92/16536 and Broger, E. A. et al., WO93/15089).

NAPHOS (6), another example of a prior art compound has been prepared (Tamao, K. et al. *Tetrahedron Lett.* **1977**, 1389) and was found to be not effective for asymmetric hydrogenation reaction. The corresponding ligands with the N linker, BDPAB (7) and H8-BDPAB (8) have also been made and tested for asymmetric hydrogenation reactions (Zhang, F. et al. *J. Am. Chem. Soc.* **1998**, 120, 5808).

## SUMMARY OF THE INVENTION

The present invention includes a ligand represented by the formula or its enantiomer:



wherein each X and X' is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>;

wherein each Z and Z<sub>1</sub> is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>; or wherein Z and Z<sub>1</sub> together form the bridging group A-B-A<sub>1</sub>;

wherein each Z', Z'', Z<sub>1</sub>' and Z<sub>1</sub>'' is independently selected from the group consisting of: H, alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>; or wherein Z' and Z together form the bridging group A'-B-A; Z' and Z together form a fused

cycloaliphatic or aromatic group;  $Z_1$  and  $Z_1'$  together form the bridging group  $A_1-B_1-A_1'$ ; and/or  $Z_1$  and  $Z_1'$  together form a fused cycloaliphatic or aromatic group;

wherein each  $A$ ,  $A'$ ,  $A_1$  and  $A_1'$  is independently selected from the group consisting of: O,  $CH_2$ , NH, NR, S, CO and a bond;

5        wherein each B and  $B_1$  is independently selected from the group consisting of: linear, branched or cyclic alkylene of 1 to 6 carbon atoms, arylene of 6 to 12 carbon atoms, O,  $CH_2$ , NH, NR, S, CO,  $SO_2$ ,  $P(O)R$ ,  $P(O)OR$ , POR,  $SiR_2$  and a bond;

      wherein each T is independently selected from the group consisting of:  
10    alkyl, substituted alkyl, aryl, substituted aryl, alkoxide, aryloxy, R,  $R'$ ,  $R''$ ,  $YR'$ ,  $YR''$ ,  $Y'R'$  and  $Y''R''$ ; or wherein two T groups together form an alkylene, arylene, alkylenediamino, arylenediamino, alkylenedioxy or arylenedioxy;

      wherein each  $T'$  is independently selected from the group consisting of:  
15    alkyl, substituted alkyl, aryl, substituted aryl, alkoxide, aryloxy, R,  $R'$ ,  $R''$ ,  $YR'$ ,  $YR''$ ,  $Y'R'$  and  $Y''R''$ ; or wherein two  $T'$  groups together form an alkylene, arylene, alkylenediamino, arylenediamino, alkylenedioxy or arylenedioxy;

      wherein each R,  $R'$  and  $R''$  is independently selected from the group consisting of: alkyl, substituted alkyl, aryl, aralkyl and alkaryl of 1 to 22 carbon atoms; or wherein two R groups, two  $R'$  groups or two  $R''$  group together form an  
20    alkylene or arene group; and

      wherein each Y,  $Y'$  and  $Y''$  is independently selected from the group consisting of: O,  $CH_2$ , NH, S and a bond between carbon and phosphorus; with the proviso that when the Y group at the 2' position is a bond between carbon and phosphorus,  $X'$  is hydrogen.

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The present invention further includes a catalyst prepared by a process, which includes: contacting a transition metal salt, or a complex thereof, and a ligand according to the present invention.

30        The present invention still further includes a process for preparation of an asymmetric compound including: contacting a substrate capable of forming an

asymmetric product by an asymmetric reaction and a catalyst prepared by a process including: contacting a transition metal salt, or a complex thereof, and a ligand according to the present invention.

5           The metal complexes are useful as catalysts in asymmetric reactions, such as, hydrogenation, hydride transfer, allylic alkylation, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, olefin metathesis, hydrocarboxylation, isomerization, cyclopropanation, Diels-Alder reaction, Heck reaction, isomerization, Aldol reaction, Michael addition, epoxidation, kinetic  
10 resolution and [m+n] cycloaddition. The metal complexes are particularly effective in Ru-catalyzed asymmetric hydrogenation of beta-ketoesters to beta-hydroxyesters and Ru-catalyzed asymmetric hydrogenation of enamides to beta amino acids.

## 15    DETAILED DESCRIPTION OF THE INVENTION

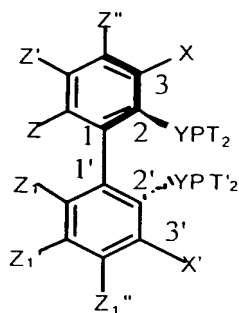
          The present invention includes 3,3'-substituted chiral biaryl phosphines and phosphinites and related ligands for applications in asymmetric catalysis. Introduction of 3,3'-substituted groups can restrict the rotation of substituents  
20 adjacent to the phosphines. Control of orientations of these groups around the phosphine can lead to effective chiral induction for asymmetric reactions. Metal complexes of these phosphines, phosphinites and related non-C<sub>2</sub> symmetric ligands with ortho substitution are useful for a large variety of asymmetric reactions. A number of chiral ligands can be made having the desired structure in  
25 which the 3,3' positions are substituted, with the proviso that at least one ortho position is occupied by a group other than H atom.

          In the non-C<sub>2</sub> symmetric ligands, ortho substituted groups play an important role for asymmetric catalysis. The 3,3' substituted chiral biaryl  
30 phosphines, phosphinites and related ligands of the present invention are

described below. An important feature of these ligands is that at least one of the 3 and 3' positions must be occupied by a group other than hydrogen.

The ligands are represented by the formula:

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wherein each X and X' is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>;

wherein each Z and Z<sub>1</sub> is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>; or wherein Z and Z<sub>1</sub> together form the bridging group A-B-A<sub>1</sub>;

wherein each Z', Z'', Z<sub>1</sub>' and Z<sub>1</sub>'' is independently selected from the group consisting of: H, alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>; or wherein Z' and Z together form the bridging group A'-B-A; Z' and Z together form a fused cycloaliphatic or aromatic group; Z<sub>1</sub> and Z<sub>1</sub>' together form the bridging group A<sub>1</sub>-B<sub>1</sub>-A<sub>1</sub>'; and/or Z<sub>1</sub> and Z<sub>1</sub>' together form a fused cycloaliphatic or aromatic group;

wherein each A, A', A<sub>1</sub> and A<sub>1</sub>' is independently selected from the group consisting of: O, CH<sub>2</sub>, NH, NR, S, CO and a bond;

wherein each B and B<sub>1</sub> is independently selected from the group consisting of: linear, branched or cyclic alkylene of 1 to 6 carbon atoms, arylene of 6 to 12

carbon atoms, O, CH<sub>2</sub>, NH, NR, S, CO, SO<sub>2</sub>, P(O)R, P(O)OR, POR, SiR<sub>2</sub> and a bond;

wherein each T is independently selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted aryl, alkoxide, aryloxy, R, R', R'', YR', YR'', Y'R' and Y''R''; or wherein two T groups together form an alkylene, arylene, alkylenediamino, arylenediamino, alkelenedioxyl or arylenedioxyl;

wherein each T' is independently selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted aryl, alkoxide, aryloxy, R, R', R'', YR', YR'', Y'R' and Y''R''; or wherein two T' groups together form an alkylene, arylene, alkylenediamino, arylenediamino, alkelenedioxyl or arylenedioxyl;

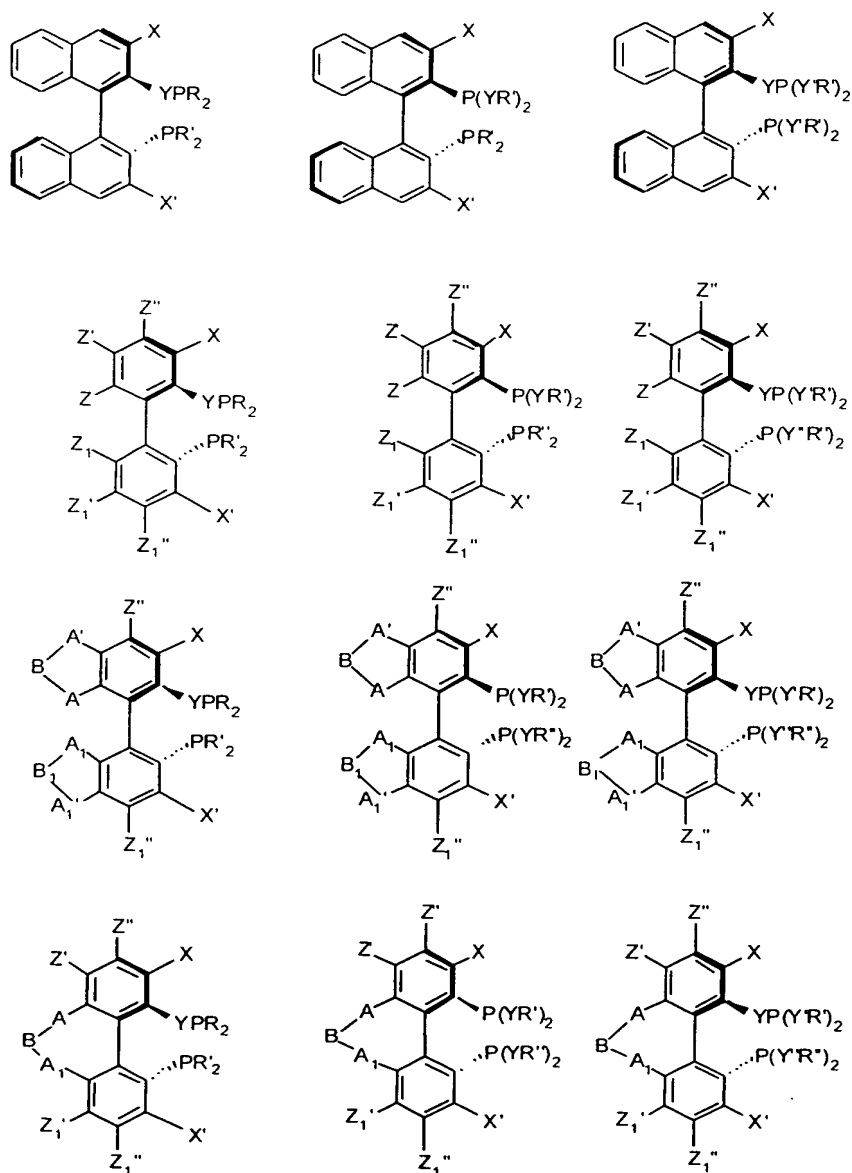
wherein each R, R' and R'' is independently selected from the group consisting of: alkyl, substituted alkyl, aryl, aralkyl and alkaryl of 1 to 22 carbon atoms; or wherein two R groups, two R' groups or two R'' group together form an alkylene or arene group; and

wherein each Y, Y' and Y'' is independently selected from the group consisting of: O, CH<sub>2</sub>, NH, S and a bond between carbon and phosphorus; with the proviso that when the Y group at the 2' position is a bond between carbon and phosphorus, X' is hydrogen. Preferably the alkylene group includes compounds represented by the formula: -(CH<sub>2</sub>)<sub>n</sub>-, wherein n is an integer in the range of from 1 to 8. The present invention also includes the corresponding enantiomer of each of the above ligands.

The substituted alkyl group can have one or more substituents and each substituent can independently be halogen, ester, ketone, carboxylic acid, hydroxy, alkoxy, aryloxy, thiol, alkylthio or dialkylamino. The aryl groups can optionally have one or more substituents, each of which can independently be halogen, ester, ketone, sulfonate, phosphonate, hydroxy, alkoxy, aryloxy, thiol, alkylthiol, nitro, amino, vinyl, substituted vinyl, carboxylic acid, sulfonic acid or phosphine. The arylene groups optionally can have one or more substituents, each of which can independently be halogen, ester, ketone, sulfonate, phosphonate, hydroxy, alkoxy, aryloxy, thiol, alkylthiol, nitro, amino, vinyl, substituted vinyl, carboxylic acid,

sulfonic acid or phosphine. Preferably, each of the arylene groups can be 1,2-divalent phenyl, 2,2'-divalent-1,1'-biphenyl, 2,2'-divalent-1,1'-binaphthyl or ferrocene, i.e., a -Fc- group.

- 5 In a preferred embodiment, the present invention includes compounds represented by the following formulas:





wherein each X and X' is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>;

5 wherein each Z and Z<sub>1</sub> is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>; or wherein Z and Z<sub>1</sub> together form the bridging group A-B-A<sub>1</sub>;

10 wherein each Z', Z'', Z'<sub>1</sub>' and Z'<sub>1</sub>'' is independently selected from the group consisting of: H, alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>; or wherein Z' and Z together form the bridging group A'-B-A; Z' and Z together form a fused cycloaliphatic or aromatic group; Z<sub>1</sub> and Z'<sub>1</sub>' together form the bridging group A<sub>1</sub>-B<sub>1</sub>-A<sub>1</sub>'; and/or Z<sub>1</sub> and Z'<sub>1</sub>' together form a fused cycloaliphatic or aromatic group;

15 wherein each A, A', A<sub>1</sub> and A<sub>1</sub>' is independently selected from the group consisting of: O, CH<sub>2</sub>, NH, NR, S, CO and a bond;

wherein each B and B<sub>1</sub> is independently selected from the group consisting of: linear, branched or cyclic alkylene of 1 to 6 carbon atoms, arylene of 6 to 12 carbon atoms, O, CH<sub>2</sub>, NH, NR, S, CO, SO<sub>2</sub>, P(O)R, P(O)OR, POR, SiR<sub>2</sub> and a bond;

20 wherein each YR', YR'', Y'R' and Y''R'' is independently selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted aryl, alkoxide and aryloxide; or wherein two YR', YR'', Y'R' or Y''R'' groups together form an alkylene, arylene, alkylenediamino, arylenediamino, alkylenedioxyl or arylenedioxyl;

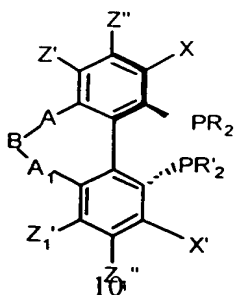
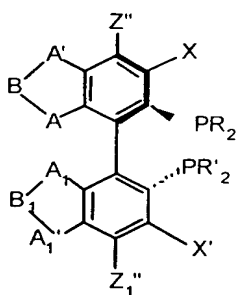
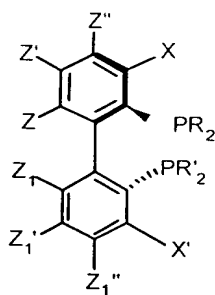
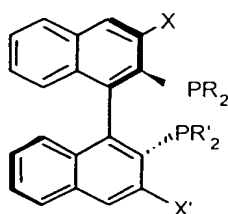
25 wherein each R, R' and R'' is independently selected from the group consisting of: alkyl, substituted alkyl, aryl, aralkyl and alkaryl of 1 to 22 carbon atoms; or wherein two R groups, two R' groups or two R'' group together form an alkylene or arelene group; and

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wherein each Y, Y' and Y'' is independently selected from the group consisting of: O, CH<sub>2</sub>, NH, S and a bond between carbon and phosphorus; with the proviso that when the Y group at the 2' position is a bond between carbon and phosphorus, X' is hydrogen.

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In another preferred embodiment, the present invention includes compounds represented by the following formulas:



wherein each X is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>;

5 wherein each X' is independently selected from the group consisting of: hydrogen, alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>;

wherein each Z and Z<sub>1</sub> is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>;

10 wherein each Z', Z'', Z<sub>1</sub>' and Z<sub>1</sub>'' is independently selected from the group consisting of: H, alkyl, aryl, substituted alkyl, substituted aryl, OR, SR, NR<sub>2</sub>, COOR, halide, SiR<sub>3</sub>, P(O)R<sub>2</sub>, P(O)(OR)<sub>2</sub> and P(OR)<sub>2</sub>;

wherein each A, A', A<sub>1</sub> and A<sub>1</sub>' is independently selected from the group consisting of: O, CH<sub>2</sub>, NH, NR, S, CO and a bond;

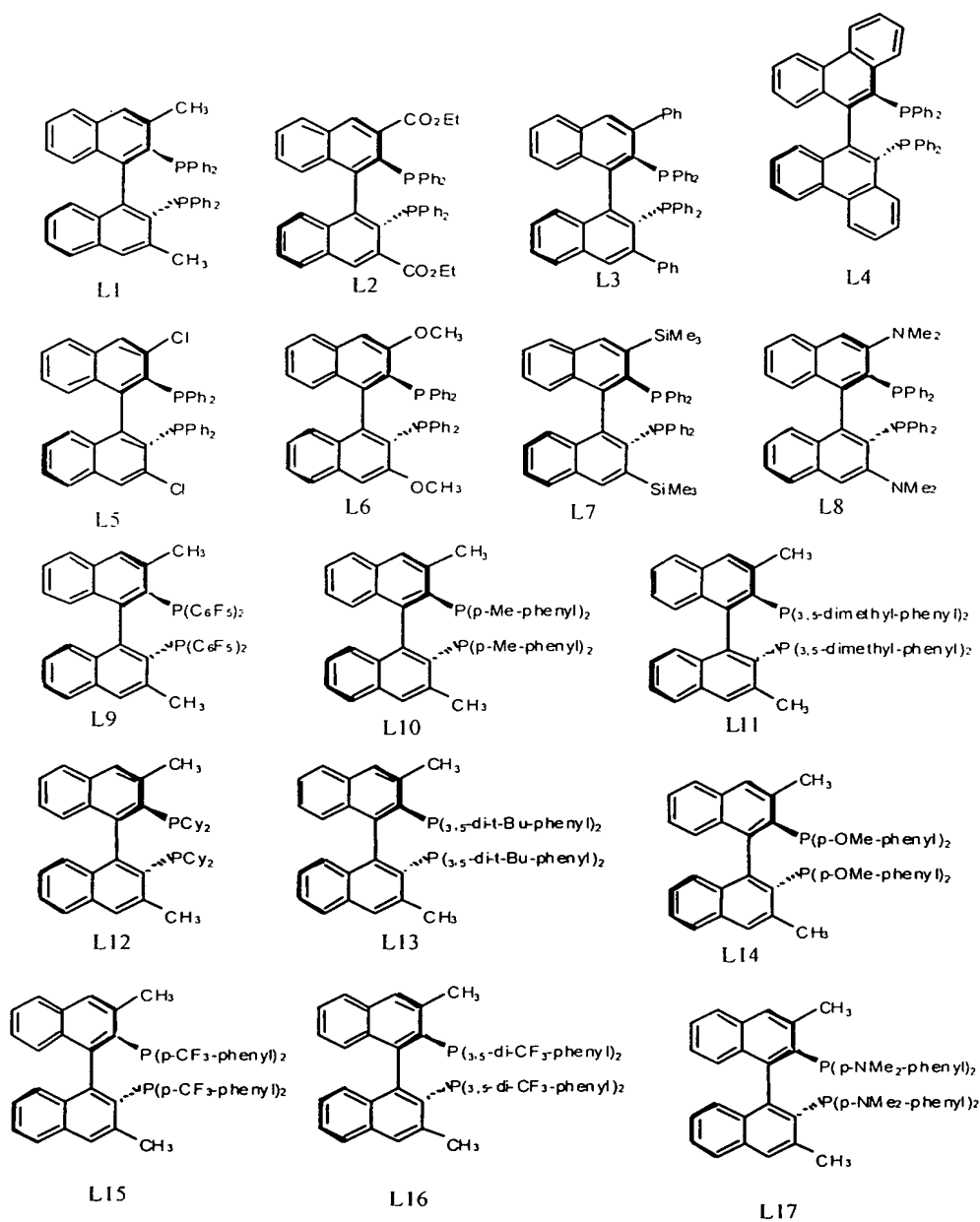
15 wherein each B and B<sub>1</sub> is independently selected from the group consisting of: linear, branched or cyclic alkylene of 1 to 6 carbon atoms, arylene of 6 to 12 carbon atoms, O, CH<sub>2</sub>, NH, NR, S, CO, SO<sub>2</sub>, P(O)R, P(O)OR, POR, SiR<sub>2</sub> and a bond;

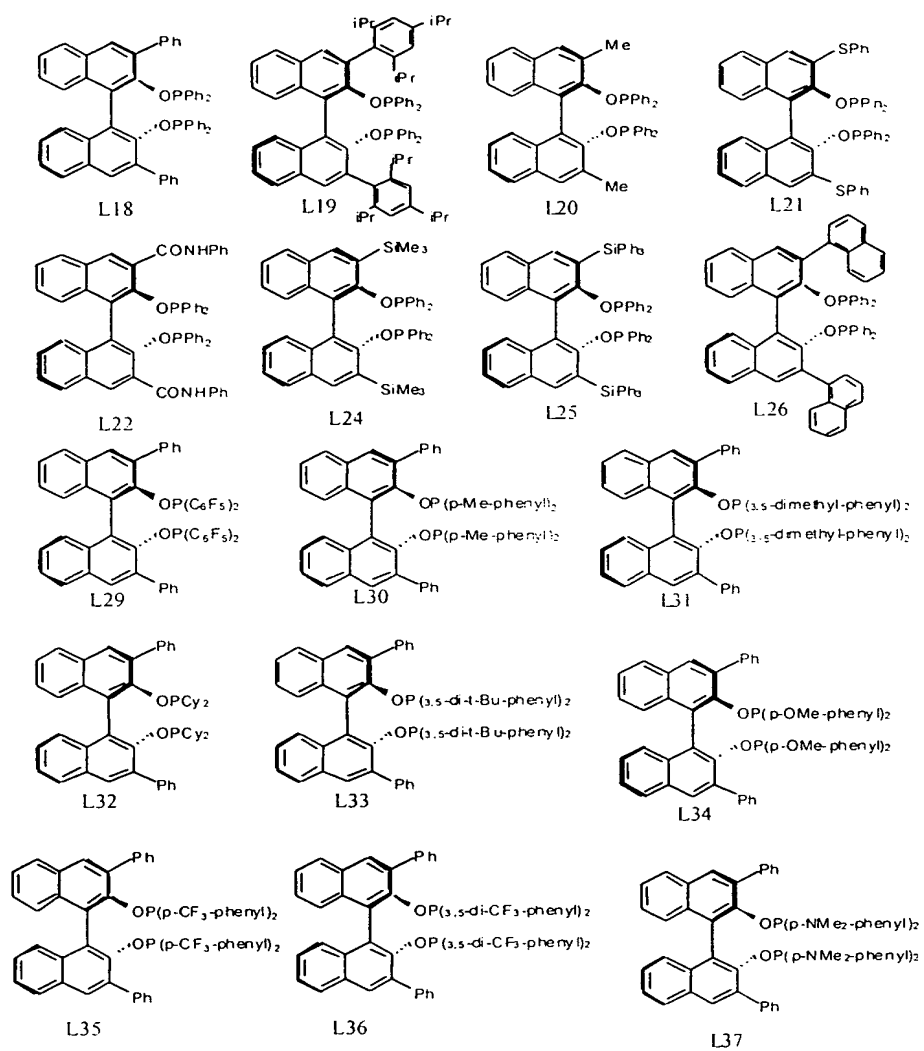
20 wherein each R and R' is independently selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted aryl, aralkyl and alkaryl of 1 to 22 carbon atoms, alkoxide and aryloxy; or

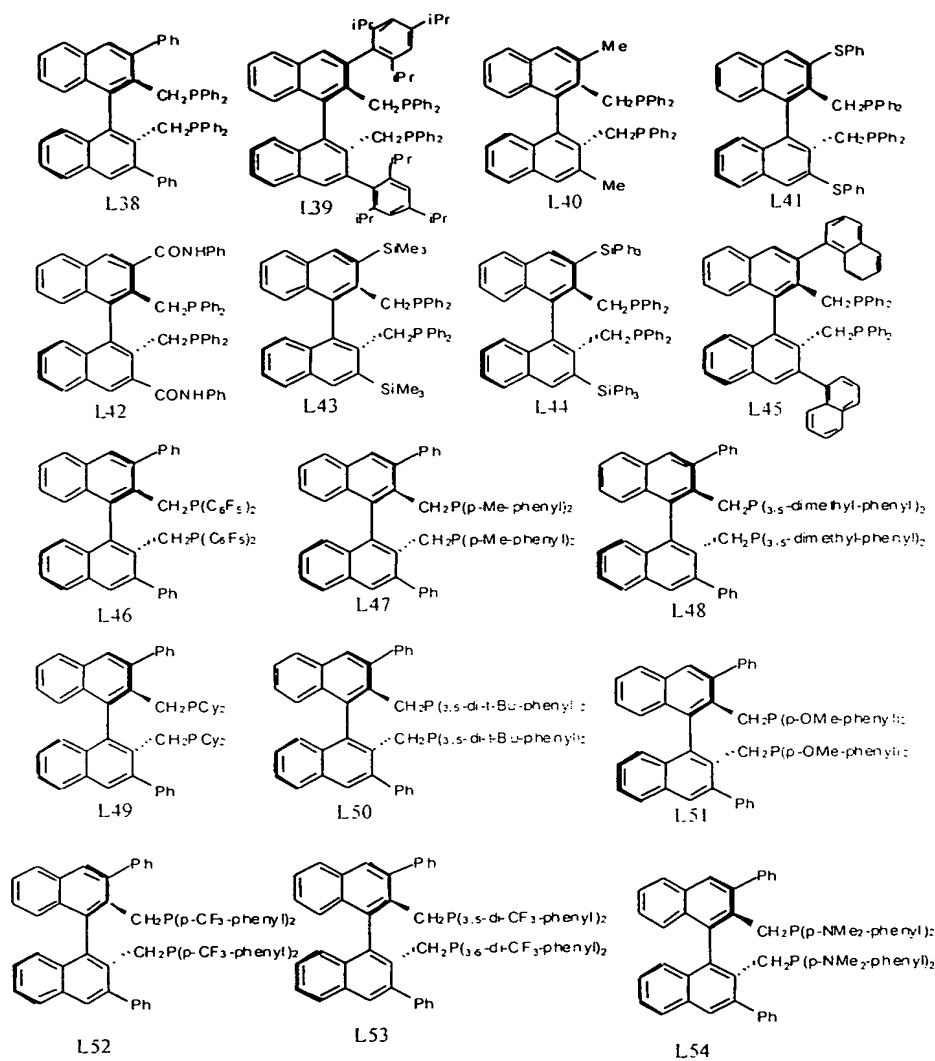
wherein two R groups or two R' groups together form an alkylene, arene, alkylenediamino, arylenediamino, alkylenedioxy or arylenedioxy groups.

The ligands of the present invention can be a racemic mixture of enantiomers. Preferably, the ligand is a non-racemic mixture of enantiomers, and more preferably, the ligand is one of the enantiomers. Preferably, the ligand has an optical purity of at least 85% ee, and more preferably, the ligand has an optical purity of at least 95% ee.

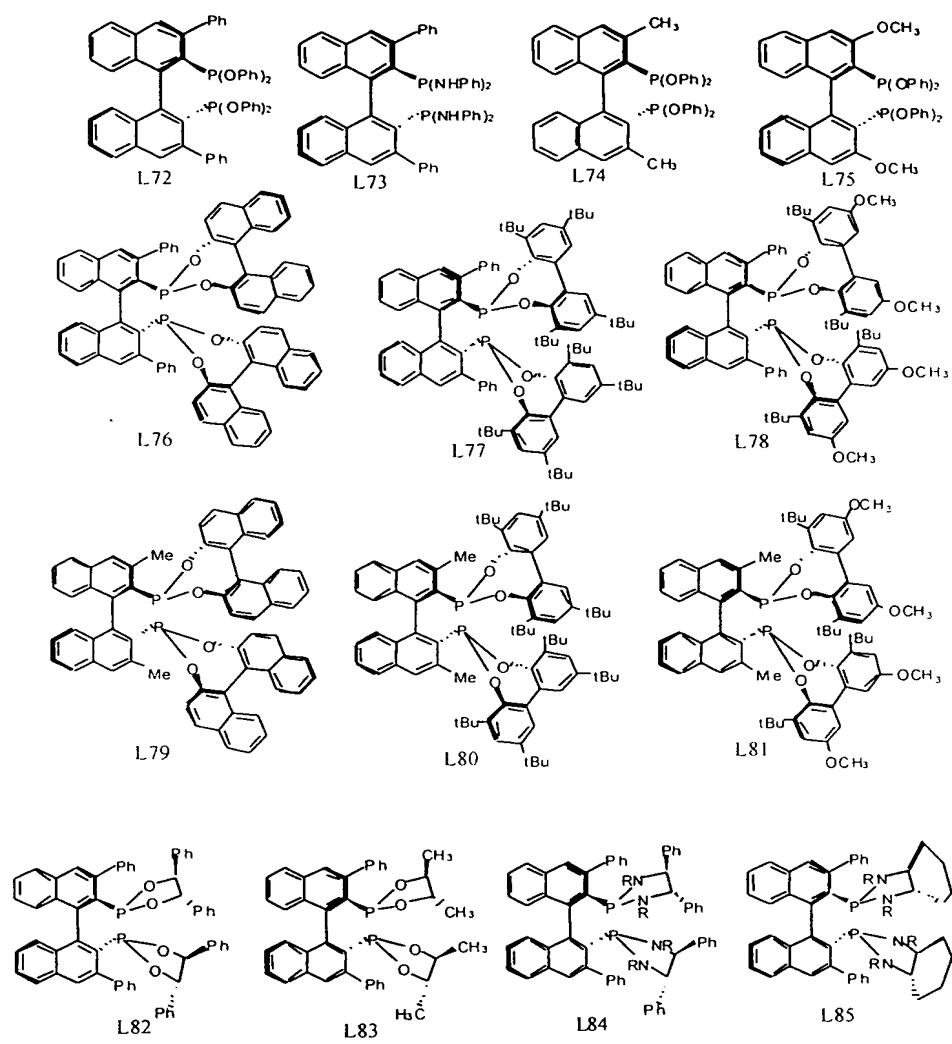
Selected examples of the chiral ligands according to the present invention are represented by the following formulas:



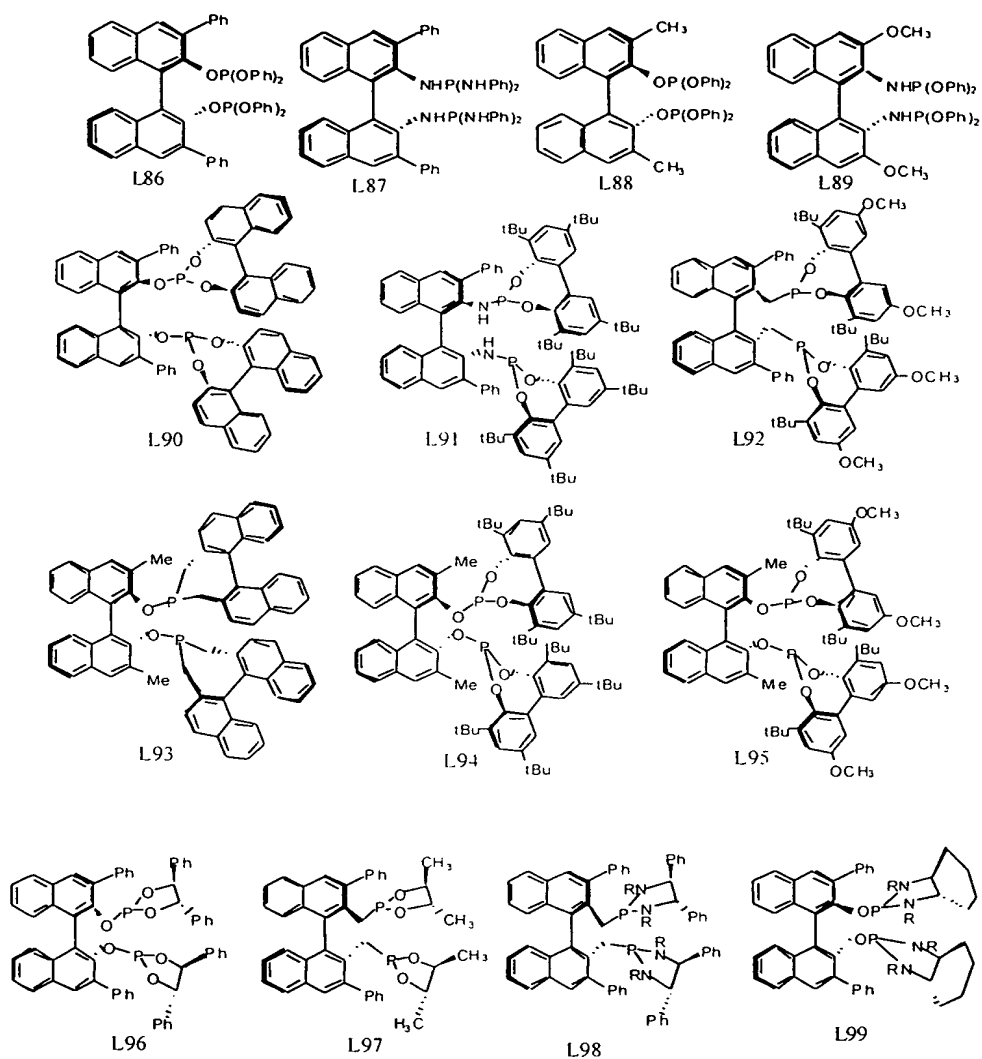




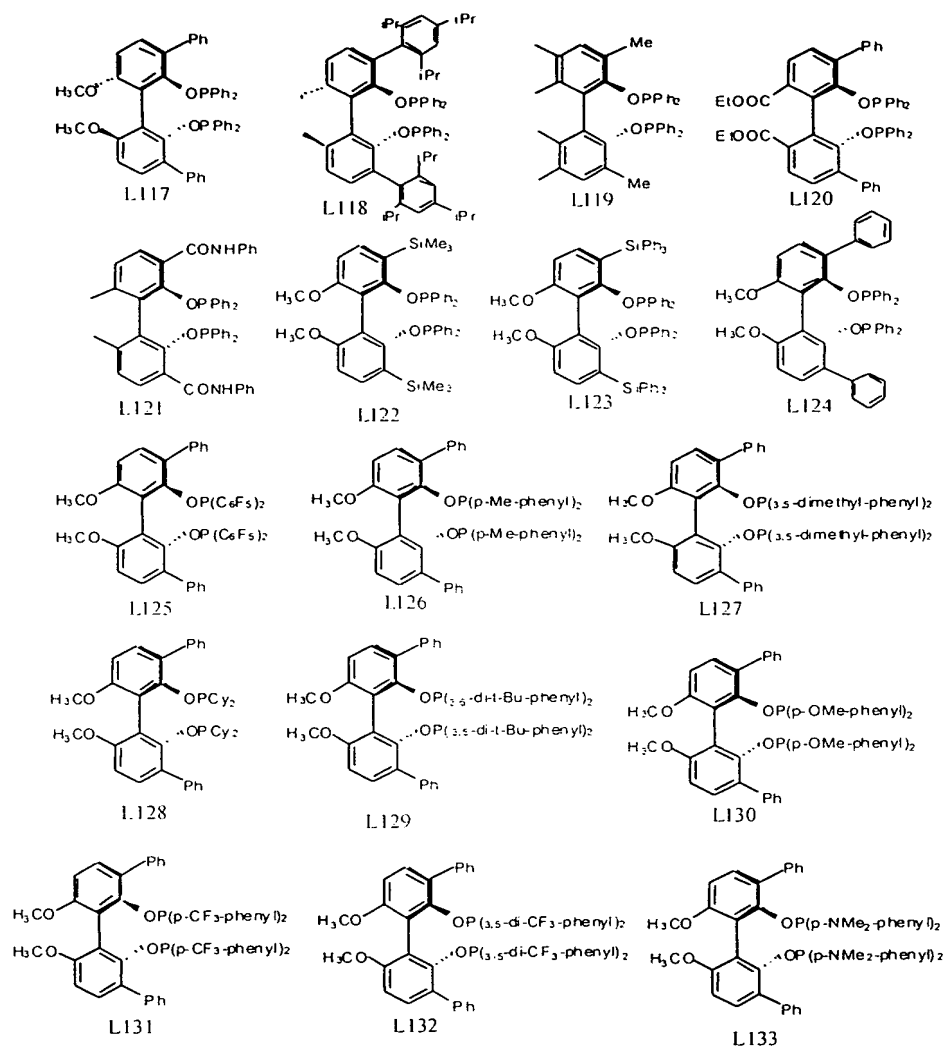


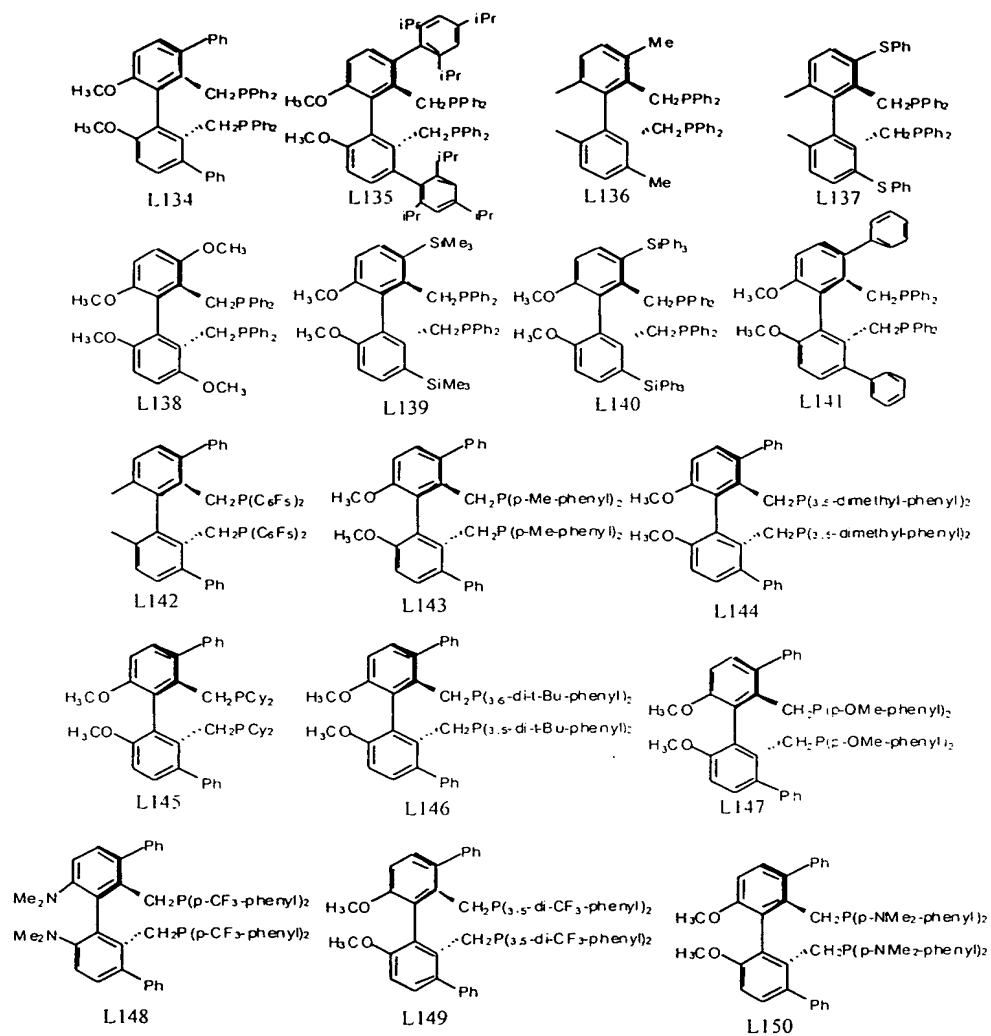


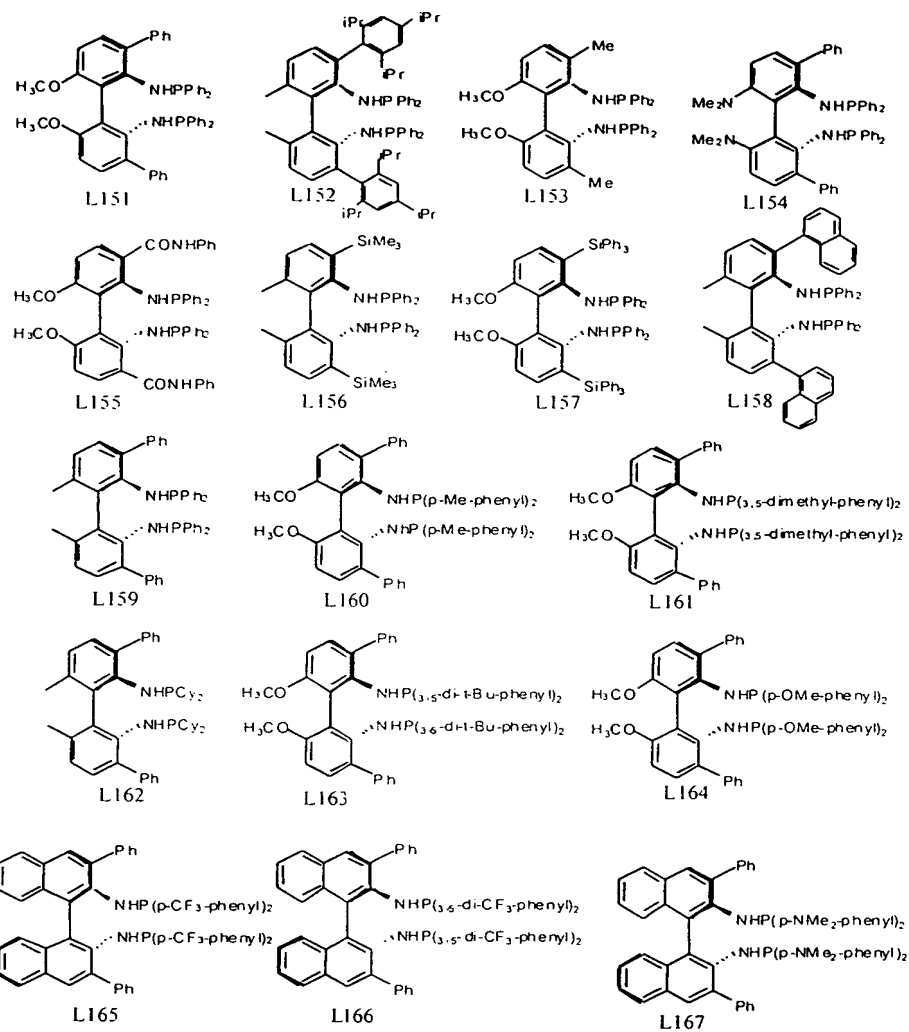


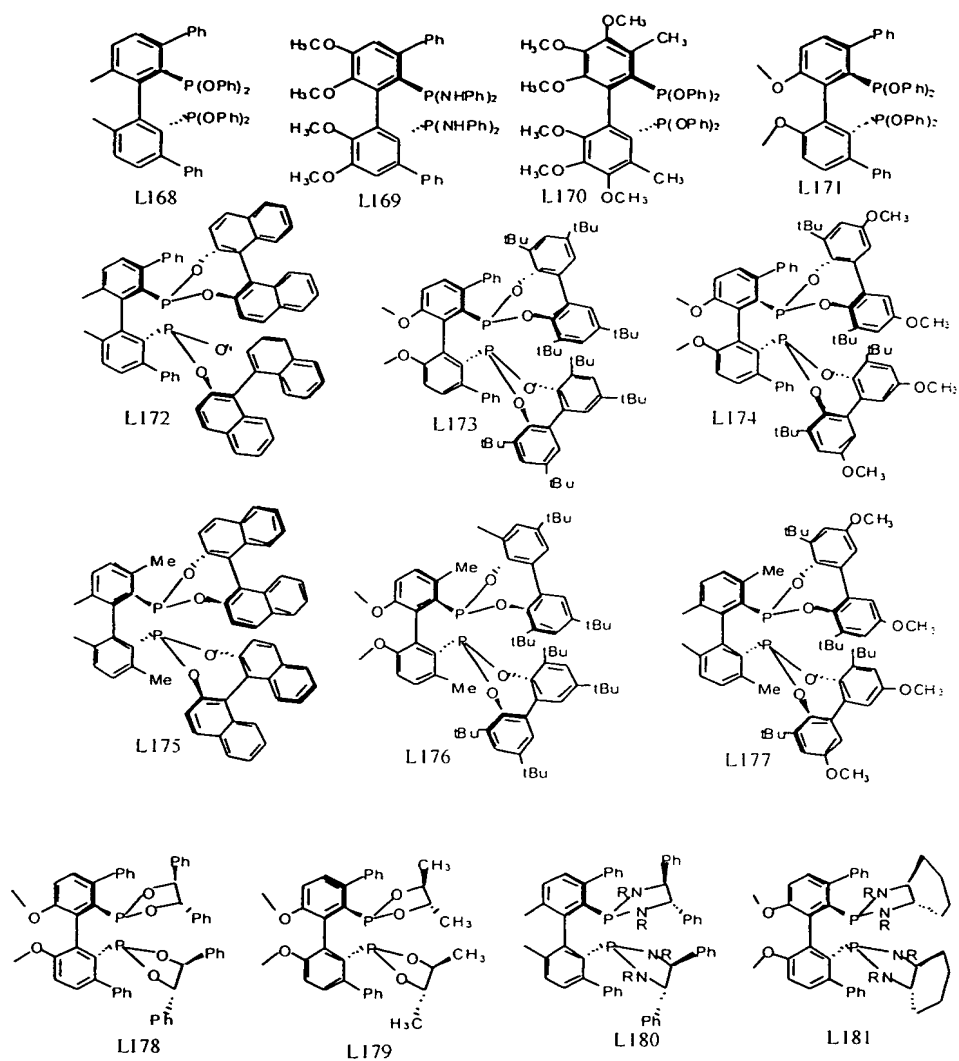


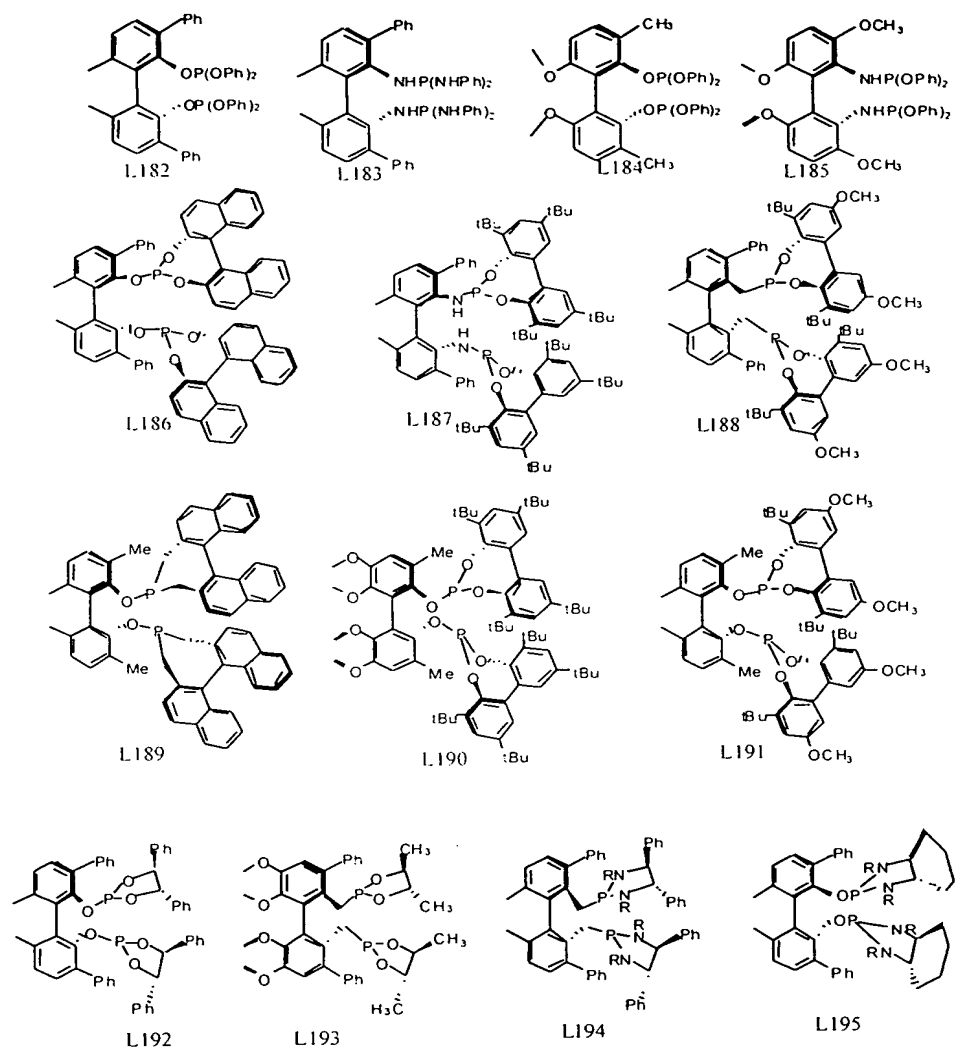


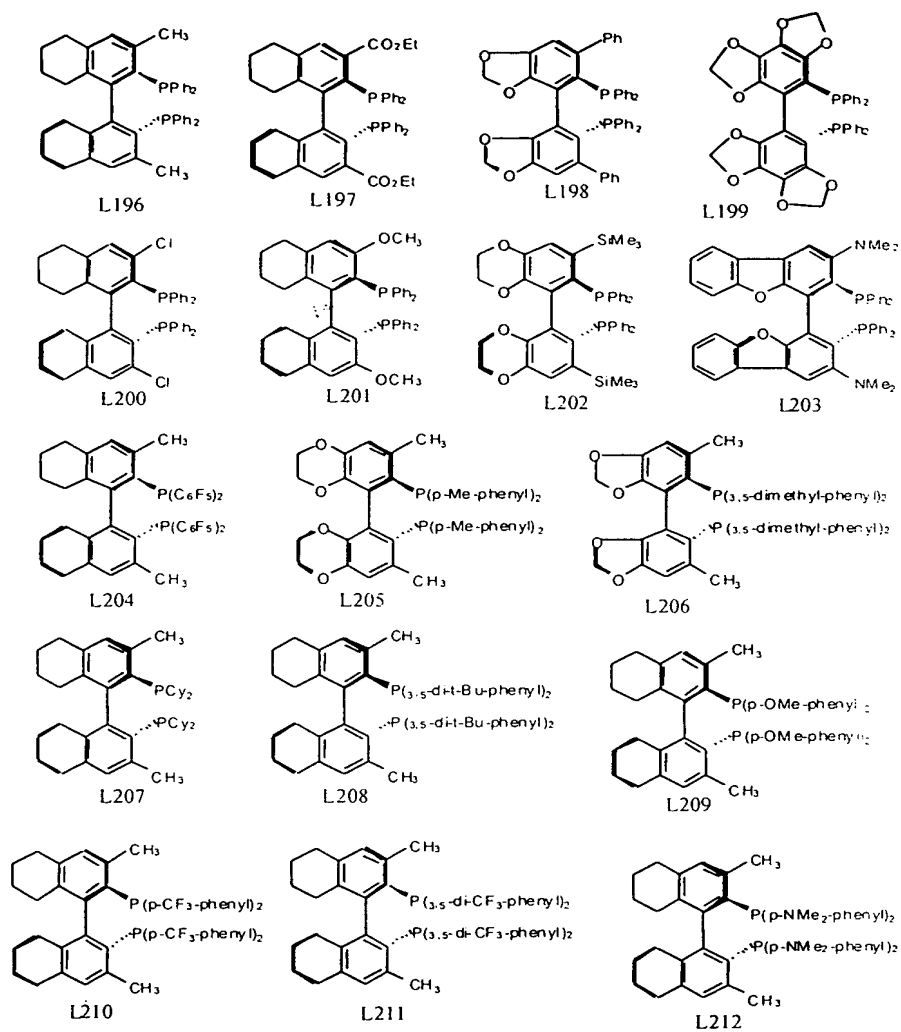




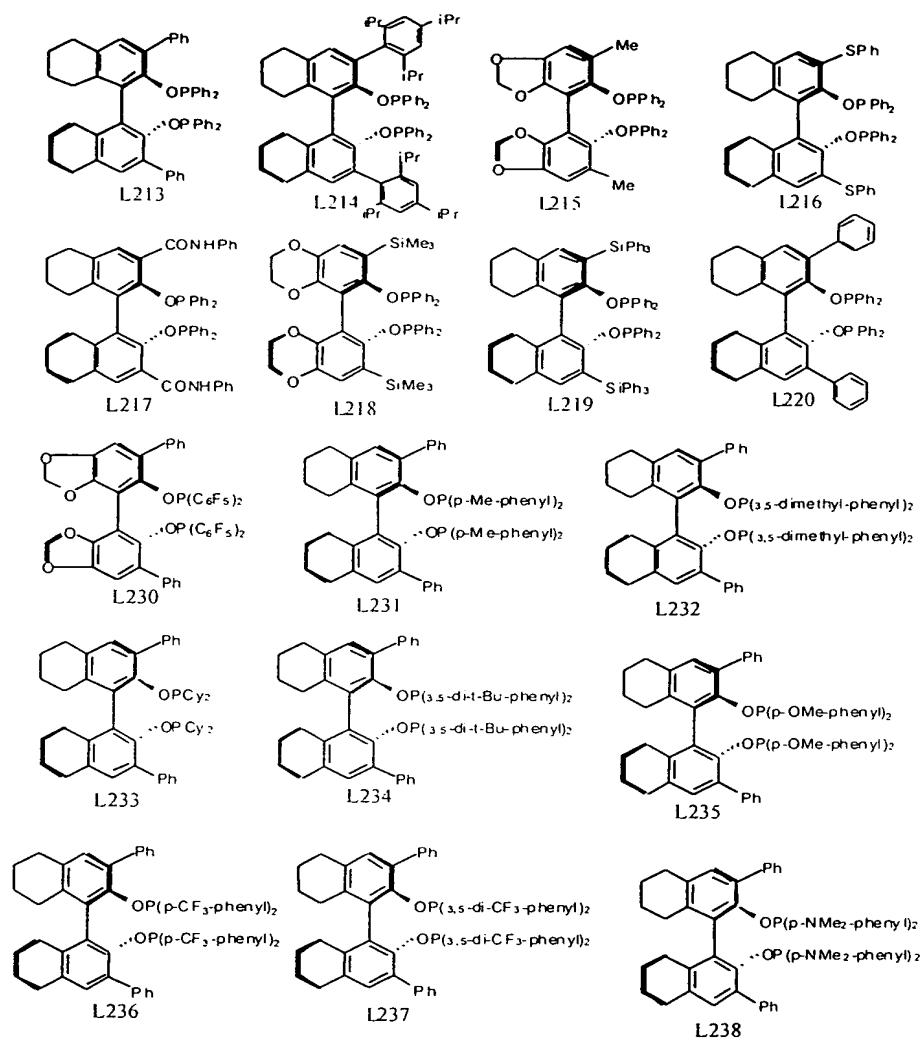


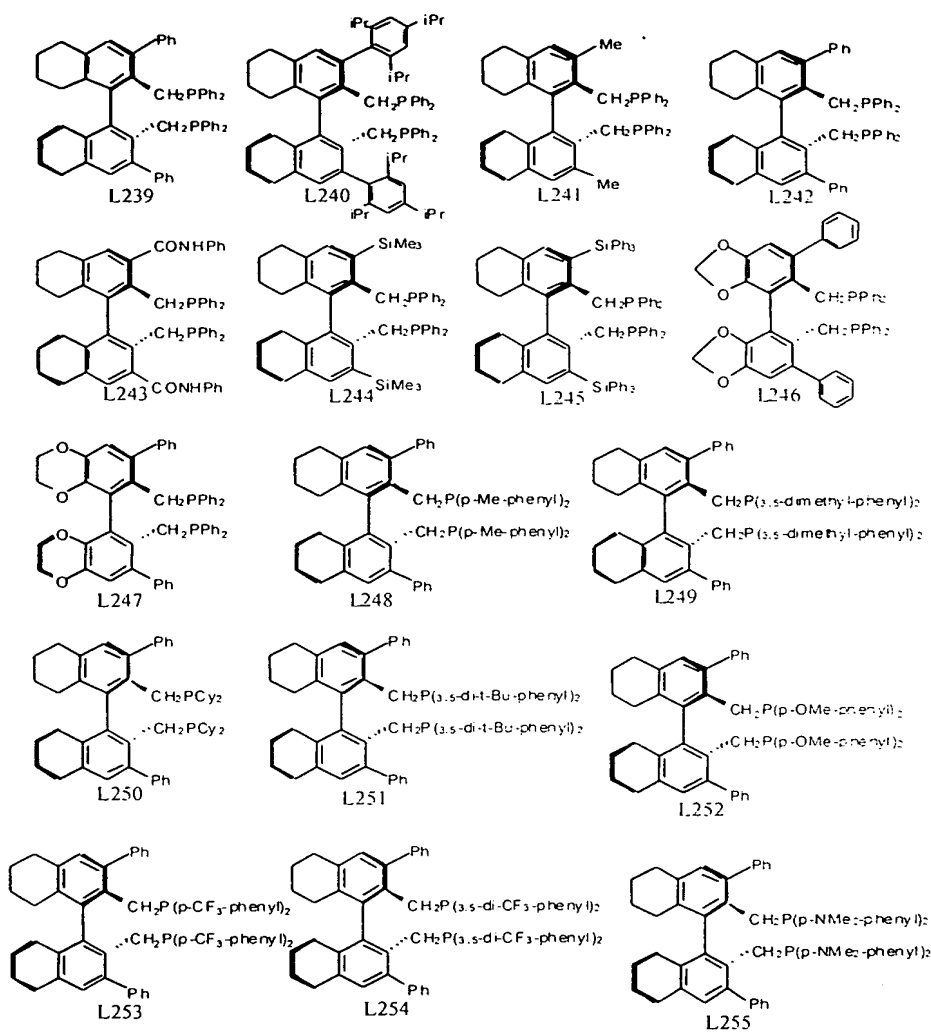


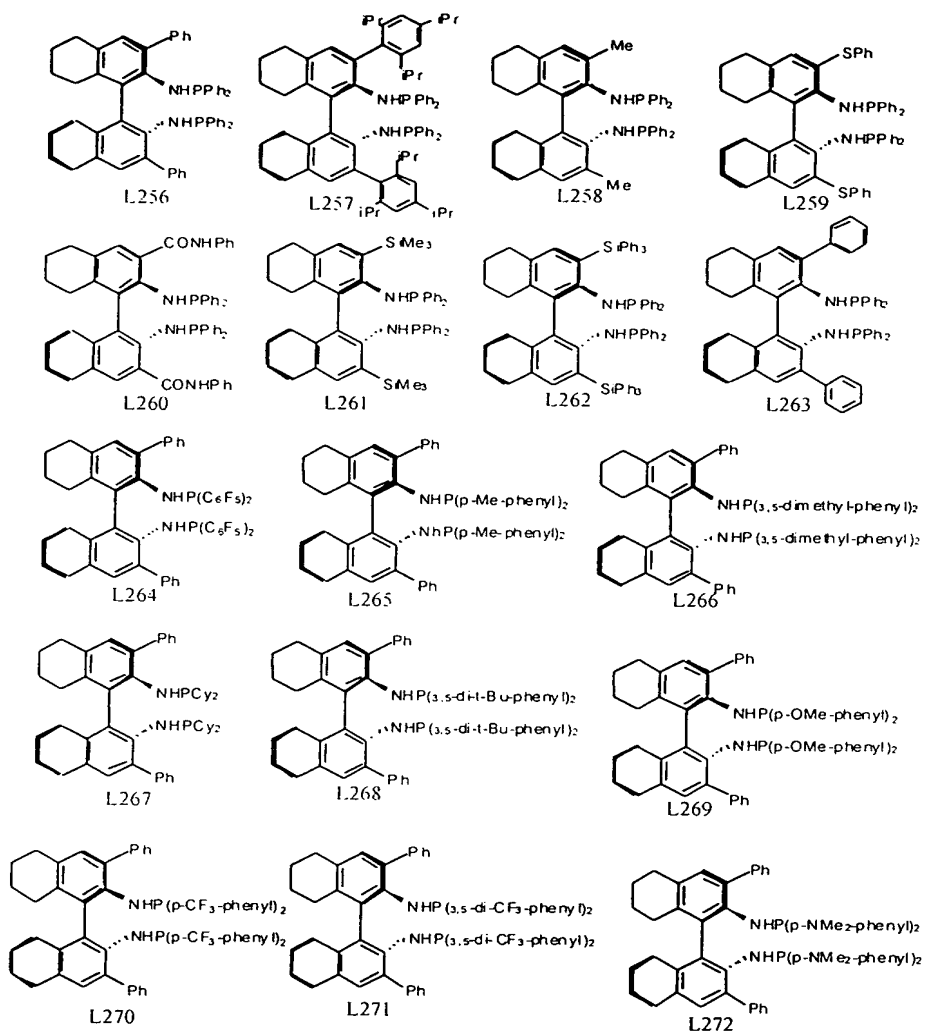


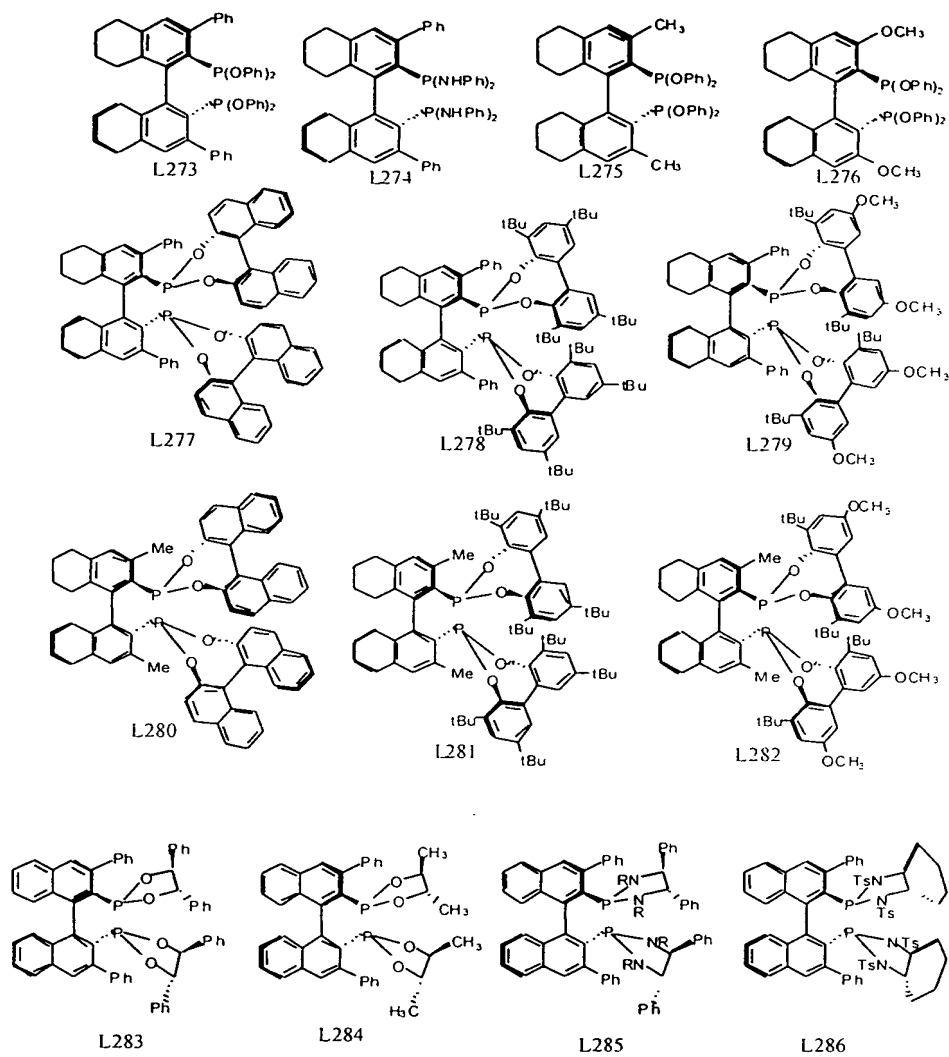


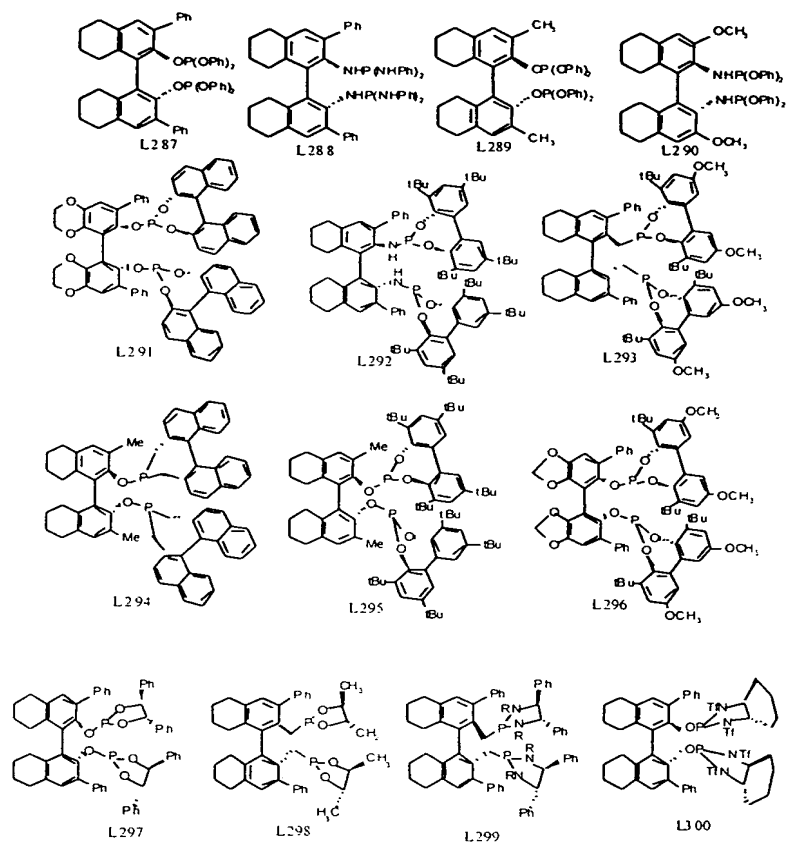


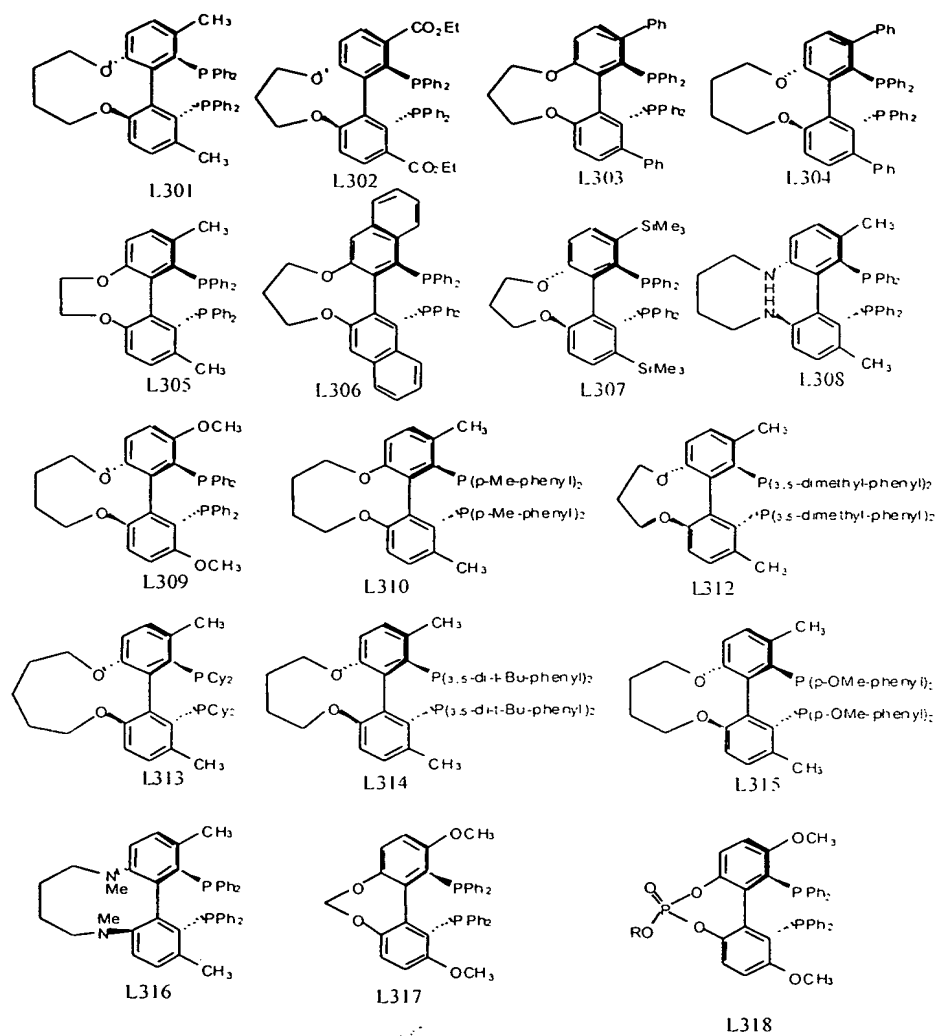




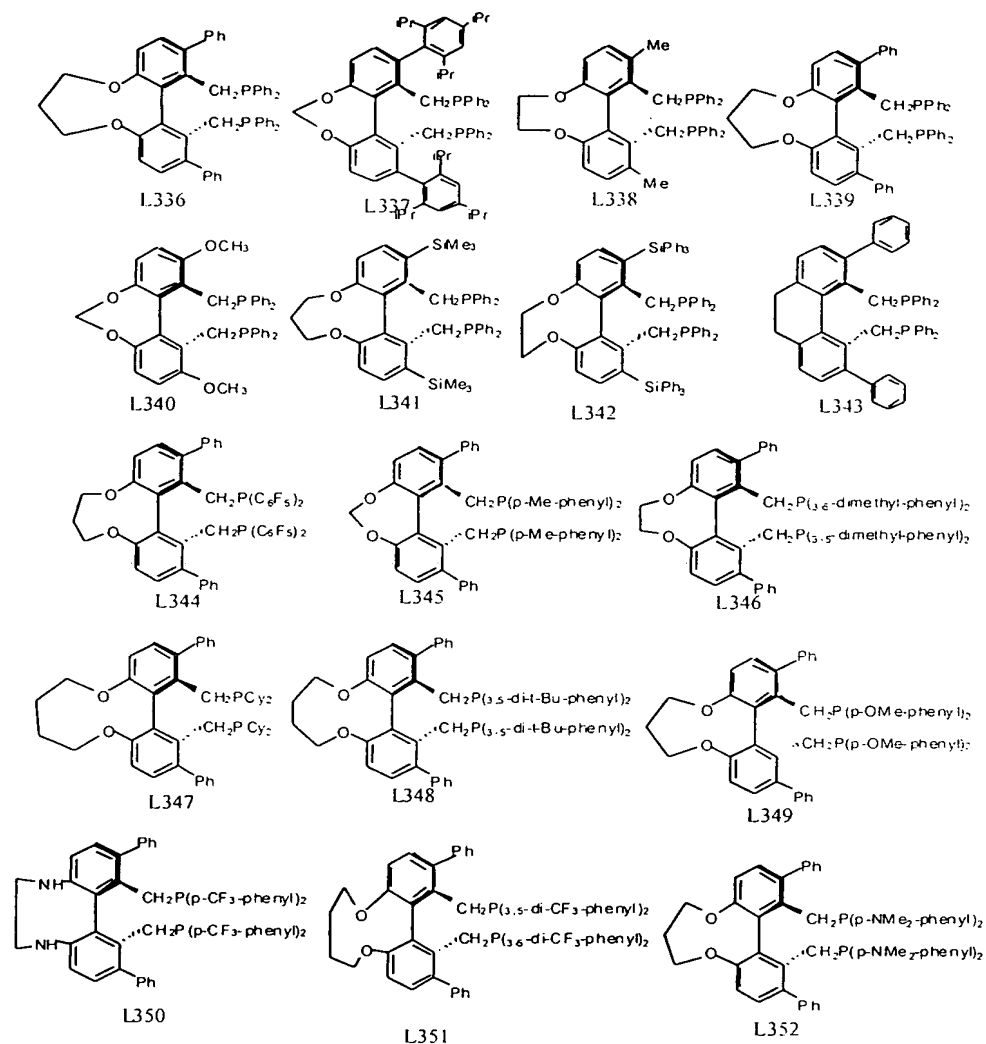




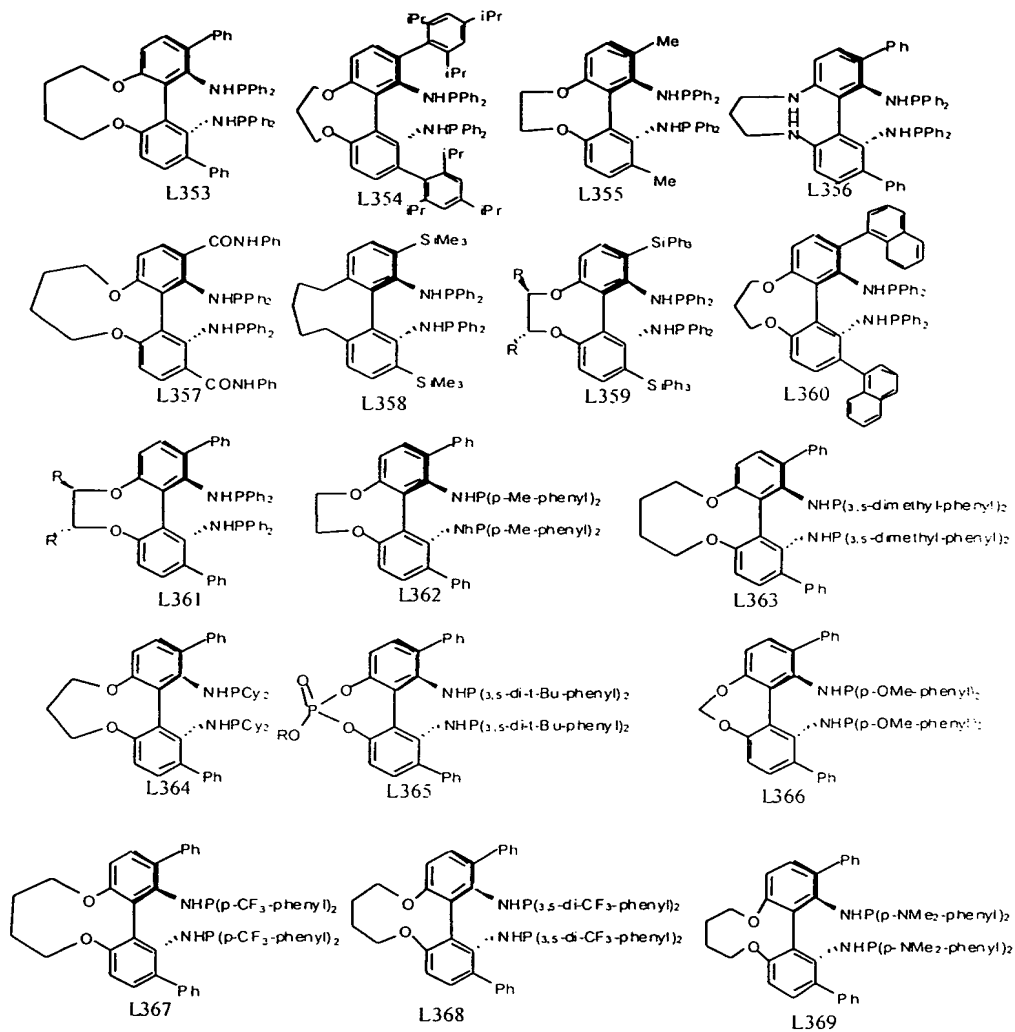


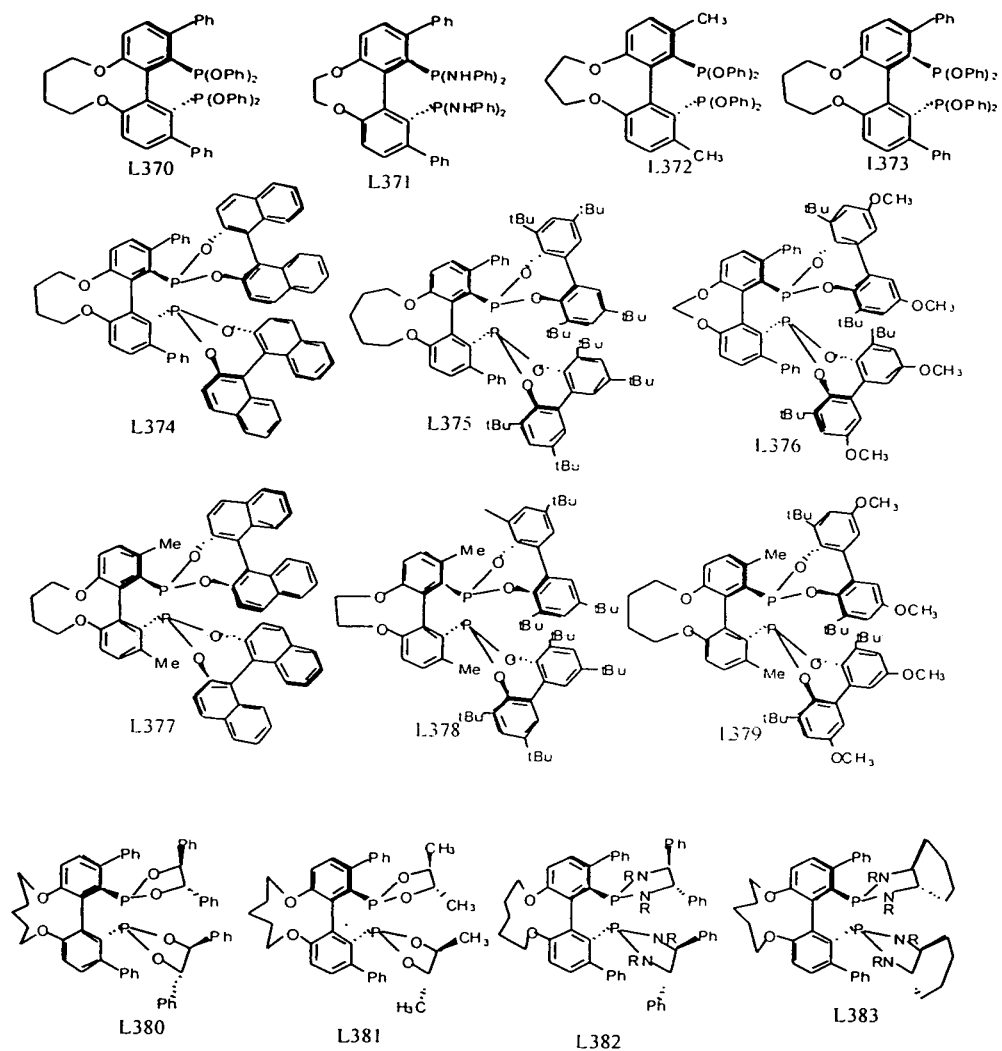


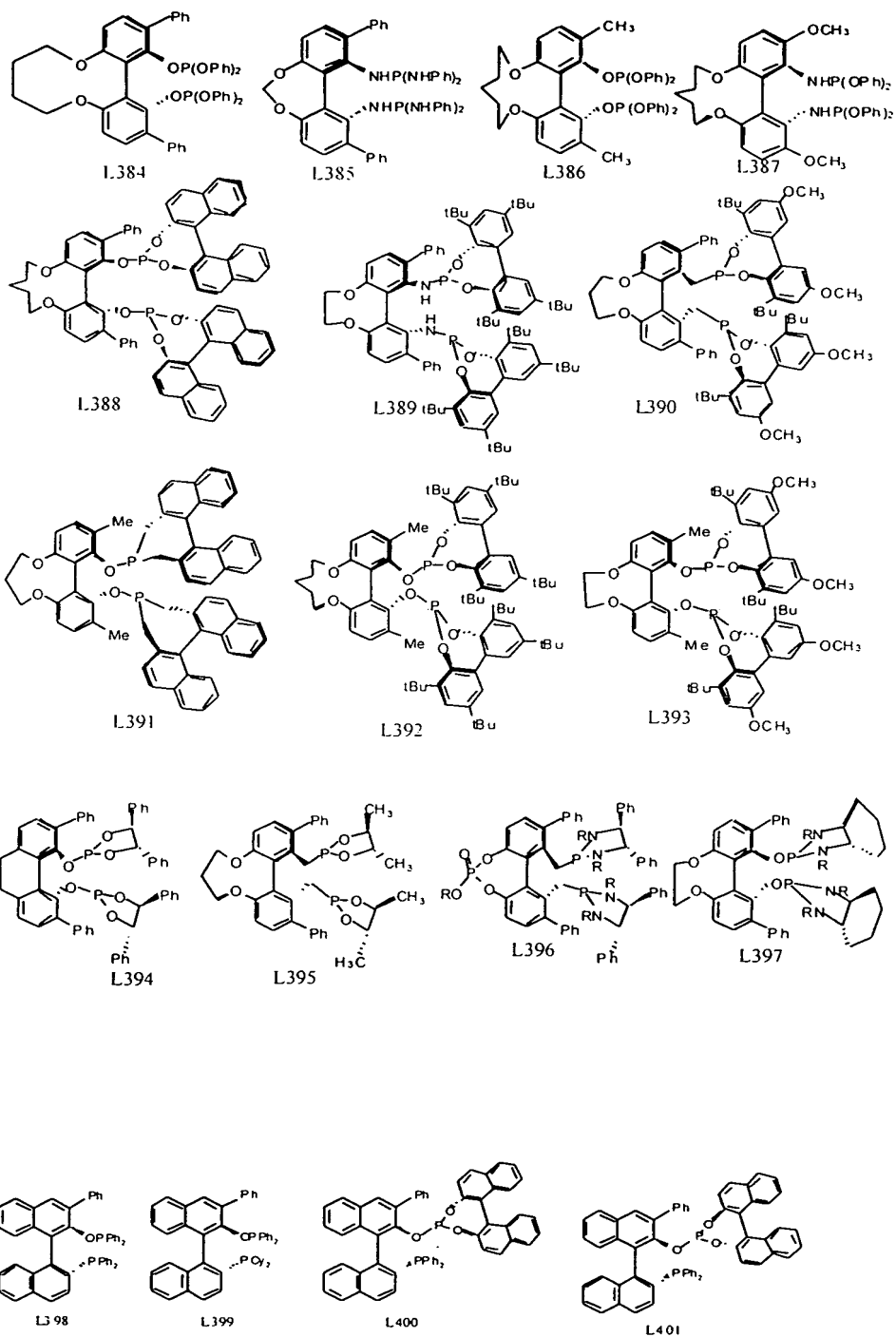












The present invention also includes a catalyst prepared by a process comprising contacting a transition metal salt, or a complex thereof, and a ligand according to the present invention. The catalyst may be prepared in situ or as an isolated compound.

The catalyst of the present invention can be a racemic mixture of enantiomers. Preferably, the catalyst is a non-racemic mixture of enantiomers, and more preferably, the catalyst is one of the enantiomers. Preferably, the catalyst has an optical purity of at least 85% ee, and more preferably, the catalyst has an optical purity of at least 95% ee.

Suitable transition metals for the preparation of the catalyst include Ag, Pt, Pd, Rh, Ru, Ir, Cu, Ni, Mo, Ti, V, Re and Mn.

As mentioned above, the catalyst can be prepared by contacting a transition metal salt or its complex and a ligand according to the present invention.

Suitable transition metal salts or complexes include the following:

AgX; Ag(OTf); Ag(OTf)<sub>2</sub>; AgOAc; PtCl<sub>2</sub>; H<sub>2</sub>PtCl<sub>4</sub>; Pd<sub>2</sub>(DBA)<sub>3</sub>; Pd(OAc)<sub>2</sub>; PdCl<sub>2</sub>(RCN)<sub>2</sub>; (Pd(allyl)Cl)<sub>2</sub>; Pd(PR<sub>3</sub>)<sub>4</sub>; (Rh(NBD)<sub>2</sub>)X; (Rh(NBD)Cl)<sub>2</sub>; (Rh(COD)Cl)<sub>2</sub>; (Rh(COD)<sub>2</sub>)X; Rh(acac)(CO)<sub>2</sub>; Rh(ethylene)<sub>2</sub>(acac); (Rh(ethylene)<sub>2</sub>Cl)<sub>2</sub>; RhCl(PPh<sub>3</sub>)<sub>3</sub>; Rh(CO)<sub>2</sub>Cl<sub>2</sub>; RuHX(L)<sub>2</sub>(diphosphine), RuX<sub>2</sub>(L)<sub>2</sub> (diphosphine), Ru(arene)X<sub>2</sub>(diphosphine), Ru(aryl group)X<sub>2</sub>; Ru(RCOO)<sub>2</sub>(diphosphine); Ru(methallyl)<sub>2</sub>(diphosphine); Ru(aryl group)X<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>; Ru(COD)(COT); Ru(COD)(COT)X; RuX<sub>2</sub>(cymen); Ru(COD)<sub>n</sub>; Ru(aryl group)X<sub>2</sub>(diphosphine); RuCl<sub>2</sub>(COD); (Ru(COD)<sub>2</sub>)X; RuX<sub>2</sub>(diphosphine); RuCl<sub>2</sub>(=CHR)(PR'<sub>3</sub>)<sub>2</sub>; Ru(ArH)Cl<sub>2</sub>; Ru(COD)(methallyl)<sub>2</sub>;

(Ir (NBD)<sub>2</sub>Cl)<sub>2</sub>; (Ir(NBD)<sub>2</sub>)X; (Ir(COD)<sub>2</sub>Cl)<sub>2</sub>; (Ir(COD)<sub>2</sub>)X; CuX (NCCH<sub>3</sub>)<sub>4</sub>; Cu(OTf); Cu(OTf)<sub>2</sub>; Cu(Ar)X; CuX; Ni(acac)<sub>2</sub>; NiX<sub>2</sub>; (Ni(allyl)X)<sub>2</sub>; Ni(COD)<sub>2</sub>; MoO<sub>2</sub>(acac)<sub>2</sub>; Ti(OiPr)<sub>4</sub>; VO(acac)<sub>2</sub>; MeReO<sub>3</sub>; MnX<sub>2</sub> and Mn(acac)<sub>2</sub>; wherein each R and R' is independently selected from the group consisting of: alkyl or aryl; Ar is an aryl group; and X is a counteranion.

In the above transition metal salts and complexes, L is a solvent and the counteranion X can be halogen, BF<sub>4</sub>, B(Ar)<sub>4</sub> wherein Ar is fluorophenyl or 3,5-di-trifluoromethyl-1-phenyl, ClO<sub>4</sub>, SbF<sub>6</sub>, PF<sub>6</sub>, CF<sub>3</sub>SO<sub>3</sub>, RCOO or a mixture thereof.

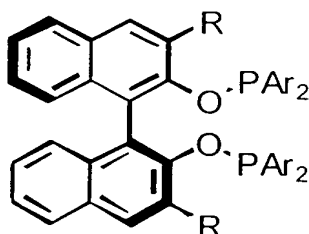
In another aspect, the present invention includes a process for preparation of an asymmetric compound using the catalysts described above. The process includes the step of contacting a substrate capable of forming an asymmetric product by an asymmetric reaction and a catalyst according to the present invention prepared by contacting a transition metal salt, or a complex thereof, and a ligand according to the present invention.

Suitable asymmetric reactions include asymmetric hydrogenation, hydride transfer, allylic alkylation, i.e., palladium-catalyzed allylic alkylation of an allylic ester, hydrosilylation, hydroboration, hydrovinylation, hydroformylation, olefin metathesis, hydrocarboxylation, isomerization, cyclopropanation, Diels-Alder reaction, Heck reaction, isomerization, Aldol reaction, Michael addition; epoxidation, kinetic resolution, i.e., palladium-catalyzed allylic alkylation of a racemic allylic ester, and [m+n] cycloaddition wherein m = 3 to 6 and n = 2, i.e., silver-catalyzed asymmetric [3 +2] cycloaddition of an azomethine ylide with a dipolarophile.

Preferably, the asymmetric reaction is hydrogenation and the substrate to be hydrogenated is an ethylenically unsaturated compound, imine, enamine, enamide, vinyl ester or a ketone, including a ketone such as a beta-ketoester.

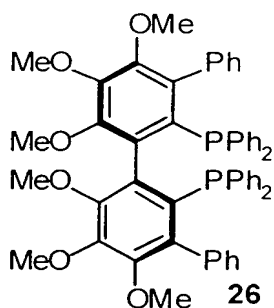
In the case of beta-ketoesters and enamides, the use of Ru as the transition metal to produce an asymmetric beta-hydroxyester and beta amino acid, respectively, is preferred, particularly when the ligand is a compound represented by one of the following formulas:

5 (a)



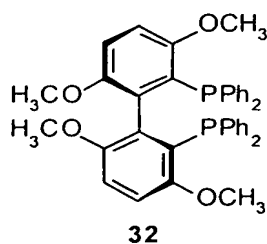
wherein each R is independently selected from the group consisting of: alkyl, aryl, substituted alkyl, substituted aryl and SiR<sub>3</sub>; and wherein each Ar is independently selected from the group consisting of: phenyl, substituted phenyl,  
10 aryl and substituted aryl;

(b)

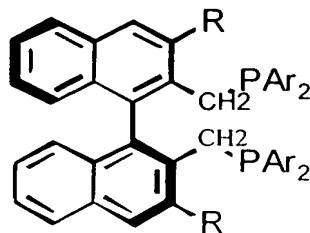


(c)

15



(d)



or a combination thereof.

5           The detailed description of ligand synthesis and asymmetric reactions thereof is provided below.

### **General procedures**

10           All reactions and manipulations were performed in a nitrogen-filled glove box or using standard Schlenk techniques. THF and toluene were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was distilled from CaH<sub>2</sub>. Methanol was distilled from Mg under nitrogen. (R, R)-BDNPB was made a solution of 10mg/ml in toluene before use. Column

15   chromatography was performed using EM silica gel 60 (230~400 mesh). <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR were recorded on Bruker WP-200, AM-300, and AMX-360 spectrometers. Chemical shifts were reported in ppm down field from tetramethylsilane with the solvent resonance as the internal standard. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. MS spectra were

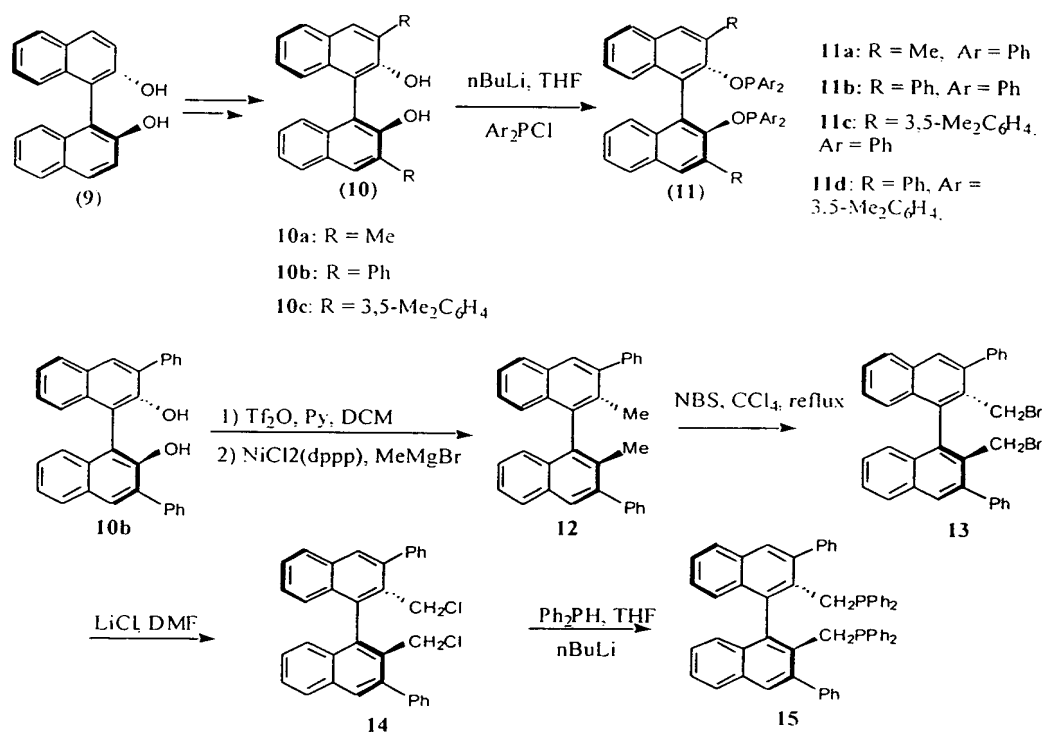
20   recorded on a KRATOS mass spectrometer MS 9/50 for LR-EI and HR-EI. GC analysis was carried on Helwett-Packard 6890 gas chromatography using chiral capillary columns. HPLC analysis was carried on Waters™ 600 chromatography.

25

### **Ligand Synthesis**

## Ligand Synthesis

Several chiral ligands have been prepared and used for asymmetric hydrogenation reactions. Scheme 1 shows the synthesis of these ligands. The starting material, enantiomerically pure BINOL can be converted to many chiral phosphines and phosphinites (**11a-L20**, **11b-L18**, **11c-L31**, **11d** and **15-L38**). 3,3'-disubstituted BINOL was prepared from (*S*)-BINOL according to known literature methods (Cox, P. J. et al. *Tetrahedron Lett.* **1992**, *33*, 2253; Simonsen, K. B. et al. *J. Org. Chem.* **1998**, *63*, 7536).



Scheme 1. Ligand Synthesis

Chiral bisphosphinite ligands (**11a-L20**, **11b-L18**, **11c-L31**, **11d**) were made through reaction of chlorodiaryl phosphine with the corresponding chiral diols (**10a-10c**) in high yields. Chiral bisphosphine **15** was made from 3,3'-diphenyl-2,3'-dihydroxyl-1,1'-binaphthyl (**10b**) in a few steps. Compounds **12-14**



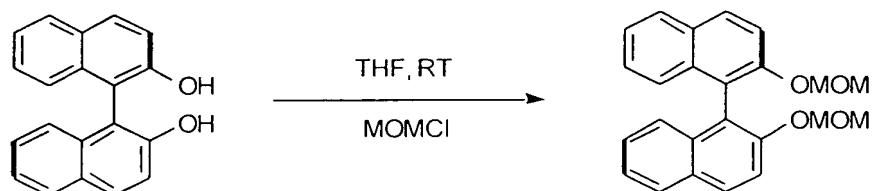
5

## EXAMPLE 1

### Synthesis of a 3,3'-Disubstituted Chiral BINOL (10b)

5

#### **(R)-2,2'-Bismethoxymethoxy-1,1'-binaphthyl**



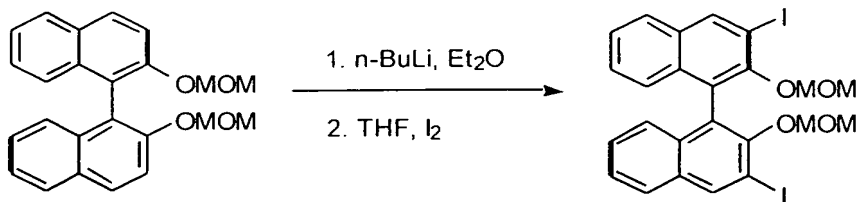
10

To a THF (200 ml) solution of NaH (5.52 g, 230 mmol) was added (R)-BINOL (28.6g, 100 mmol) solution in THF (50 ml) under nitrogen at zero temperature, after 30 min. chloromethyl methyl ether (17.09 ml, 225 mmol) in 30 ml THF was added dropwise. The mixture was stirred overnight at room

15 temperature. 3 ml water was added carefully to destroy the excess NaH, and filtered to remove the inorganic salt. The solution was passed a silica gel plug (hexane/ethyl acetate = 1/1) to give pure product (97% yield).

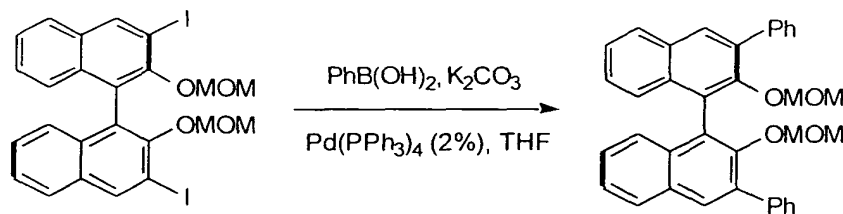
#### **(R)-3,3'-diiodo-2,2'-Bismethoxymethoxy-1,1'-binaphthyl**

20

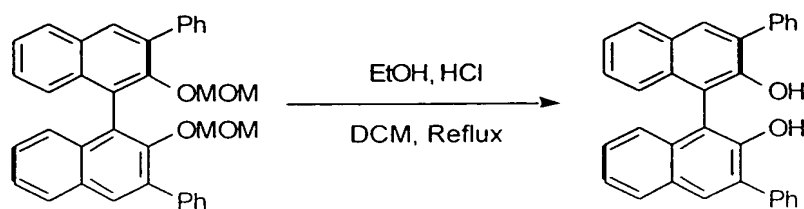


To a solution of (R)-2,2'-Bismethoxymethoxy-1,1'-binaphthyl (37.4g, 100mmol) in diethyl ether (400 ml) was added *n*-BuLi (100 ml, 2.5 M in hexane, 250 mmol) at room temperature under nitrogen, the mixture was stirred for 3 hours, then was cooled to 0°C, 200 ml THF was added, after 10 min, a solution of iodine (300 mol, 76.2g) in THF (60 ml) was added dropwise. The mixture was allowed to warm to room temperature over 4 hours. 100 ml saturated Na<sub>2</sub>SO<sub>3</sub> aqueous was added to destroy the excess iodine, then extracted with ethyl acetate, organic phase was washed with 100 ml saturated Na<sub>2</sub>SO<sub>3</sub>, 3X100 ml water, dried over sodium sulfate and evaporated. The residue was purified by a silica gel column eluted with (hexane /ethyl acetate = 7/1) to give product as a yellow solid (80% yield, contain 5-7% monoiodo-substituted product).

**(R)-3,3'-diphenyl-2,2'-Bismethoxymethoxy-1,1'-binaphthyl**



To a solution of (R)-3,3'-diiodo-2,2'-Bismethoxymethoxy-1,1'-binaphthyl (90 mmol, 56.3g) and phenylboronic acid (25.2 g, 225 mmol) in THF 800 ml, was added Pd(PPh<sub>3</sub>)<sub>4</sub> (2.3 g, 2 mmol) and degassed 1M K<sub>2</sub>CO<sub>3</sub> aqueous solution (400 ml, 400 mmol). The reaction mixture was heated at reflux for 20 hours. The mixture was extracted with ethyl acetate, and combined organic layer was washed with brine. Evaporation of the solvent gave a yellow solid (47g). The residue was used to next step without other purification.



5

### **(R)-3,3'-diphenyl-1,1'-binaphthol**

To a solution of (R)-3,3'-diphenyl-2,2'-Bismethoxymethoxy-1,1'-binaphthyl (47 g) in a mixture solvent of 200 ml DCM and 500 ml EtOH was added concentrated HCl (90 ml). The reaction mixture was heated at reflux under nitrogen for 16 hours. The volatile components were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (DCM/hexanes=4/6) to give the product (25.2 g, 57.6 mmol, 64% yield for two steps)

15

## **EXAMPLE 2**

### **Alternative Route for the Synthesis of a 3,3'-Disubstituted Chiral BINOL (10b)**

20

### **(S)-2,2'-Dimethoxy-1,1'-dinaphthyl**

To a solution of (S)-2,2'-dihydroxy-1,1'-dinaphthyl (100g, 349.7 mmol) in 1000ml 95% EtOH was added dimethyl sulfate (93.1ml, 981.7 mmol, 2.8eq.) and followed by dropwise addition of a solution of NaOH (175g) in 300ml H<sub>2</sub>O. After the addition, the resulting system was heated to reflux for 3 h, and then cooled. The reaction mixture was filtered, the precipitate was collected and

25

washed with 10% aqueous NaOH (3×150 ml), and recrystallized from toluene (reflux to dissolve into 700 ml toluene, then let it stay at 0 °C overnight) to yield 84.1g white crystal product (S)-2,2'-dimethoxy-1,1'-dinaphthyl (yield = 76.6%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.985(d, *J*=9.0Hz, 2H, Ar-H), 7.875(d, *J*=8.1Hz, 2H, Ar-H),  
5 7.468(d, *J*=9.0Hz, 2H, Ar-H), 7.300~7.326(t, 2H, Ar-H), 7.199~7.218(t, 2H, Ar-H), 7.118(d, *J*=8.1Hz, 2H, Ar-H), 3.773(s, 6H, -OCH<sub>3</sub>).

**(S)-3,3'-Bis(dihydroxyborane)-2,2'-Dimethoxy-1,1'-dinaphthyl**

10 Under N<sub>2</sub>, in a 500 ml Schlenk flask were placed 300 ml of dry *t*-butyl-methyl ether and TMEDA (14.4 ml, 95.5 mmol, 3equiv). To this solution was added 2.5M *n*-BuLi in hexane(39.5 ml, 98.7 mmol, 3.1 equiv), the resulting solution was stirred for 30 min. at room temperature, solid (S)-2,2'-dimethoxy-1,1'-dinaphthyl (10g, 31.8mmol) was added in one portion under N<sub>2</sub> flow, the  
15 reaction system was stirred at room temperature for 3hrs. The resulting brown slurry was cooled to -78°C, and B(OEt)<sub>3</sub> (33.9 ml, 197.5 mmol, 6.2equiv) was dropwise introduced over a period of 15min. The reaction system was allowed to warm room temperature and was left stirring overnight. The reaction was quenched with 150ml aqueous 1M HCl solution, and was stirred for another 2 h.  
20 The phase was separated, the organic phase was washed with aqueous 1M HCl solution (3 × 100mL) and saturated aqueous NaCl solution (3 × 100 ml), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed, and the resulting white solid were recrystallized twice from 70ml toluene (reflux to dissolve into 700ml toluene, then let it stay at 0 °C overnight, and recrystallization once can't remove by-product  
25 completely) to give the product (S)-3,3'-Bis(dihydroxyborane)-2,2'-Dimethoxy-1,1'-dinaphthyl 9.33g (Yield = 73.3%).<sup>1</sup>H-NMR(Acetone-*d*<sub>6</sub>): δ 8.556(s, 2H, Ar-H), 8.041(d, *J*=8.1Hz, 2H, Ar-H), 7.454(t, 2H, Ar-H), 7.335(t, 2H, Ar-H), 7.112(d, *J*=8.1Hz, 2H, Ar-H), 3.773(s, 6H, -OCH<sub>3</sub>).<sup>1</sup>H-NMR shows that toluene is very difficult to remove completely, but there is no any influence on the  
30 secondary reaction.

### **(S)-3,3'-Diphenyl-2,2'-dimethoxy-1,1'-dinaphthyl**

5            In a 50ml Schlenk flask were placed (S)-3,3'-bis(dihydroxyborane)-2,2'-  
dimethoxy-1,1'-dinaphthyl(1.206 g, 3 mmol), Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (2.739g, 8.7mmol,  
2.9 equiv), and Pd(PPh<sub>3</sub>)<sub>4</sub> (183 mg, 0.15 mmol, 5% mol), the reaction system was  
evacuated and filled with N<sub>2</sub> for three times, 1,4-dioxane(18ml), H<sub>2</sub>O(8ml), and  
bromobenzen(1.89ml,18mmol, 6eq.) were added. The reaction system was heated  
10        under reflux for 24 hrs under N<sub>2</sub> and cooled to room temperature. The 1,4-dioxane  
was removed, and the resulting mixture was redissolved into 100ml CH<sub>2</sub>Cl<sub>2</sub>, and  
washed with aqueous 1M HCl solution (3× 50 ml) and saturated aqueous NaCl  
solution(2 × 50 ml), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed to yield  
crude product (S)-3,3'-diphenyl-2,2'-dimethoxy-1,1'-dinaphthyl 1.513 g as orange  
15        syrup.

This intermediate was not isolated and was used directly in the final step.

### **(S)-3,3'-Diphenyl-2,2'-dihydroxy-1,1'-dinaphthyl (10b)**

20            The crude product diphenyl-2,2'-dimethoxy-1,1'-dinaphthyl (1.513g,  
approximately 3mmol) was dissolved into 80 ml dry CH<sub>2</sub>Cl<sub>2</sub>, and cooled to -78°C,  
BBr<sub>3</sub>( 1.5 ml) was added in 10 min., and the reaction system was stirred for 18 h  
at room temperature. The resulting slight brown solution was cooled to 0°C, and  
25        200 ml H<sub>2</sub>O was added carefully. The phase was separated, and the organic phase  
was washed with H<sub>2</sub>O (5 × 80 ml) and saturated aqueous NaCl solution (2 × 50  
ml), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed, and the resulting solid was  
recrystallized from 10 ml MeOH to yield (S)-10b as white-gray powder (overall  
yield of coupling and deprotection steps, 61.8%).

30

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 8.029(s, 2H, Ar-H), 7.929(d, *J* = 7.9 Hz, 2H, Ar-H), 7.741(dd, 4H, *J* = 7.9, 1.4 Hz, Ar-H), 7.499(t, 4H, Ar-H), 7.376~7.434 (m, 4H, Ar-H), 7.325 (td, 2H, *J* = 7.9, 1.3 Hz, Ar-H), 7.250(t, 2H, Ar-H), 5.364(br, 2H, -OH).

5

### EXAMPLE 3

#### Synthesis of a 3,3'-Disubstituted Chiral Phosphinite, (R)-3,3'-diphenyl-2,2'-bis(diphenylphosphinoxy)-1,1'-binaphthyl (11b)

10

To a solution of (*R*)-3,3'-diphenyl-1,1'-binaphthol (876 mg, 2 mmol) in 20 ml THF at -78°C was added *n*-BuLi (2.8 ml, 4.5 mmol) dropwise, the mixture was warmed to room temperature and stirred for 30 min, then cooled to -78°C, Ph<sub>2</sub>PCl (0.9 ml, 5 mmol) was added *via* syringe, then warmed to room temperature and stirred overnight. The THF was removed under reduced pressure, the residue was purified by basic Al<sub>2</sub>O<sub>3</sub> (EtOAc/Hexane/Et<sub>3</sub>N = 90/8/2) to give pure product (1.41 g, 87% yield).

15

<sup>1</sup>H-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 360 MHz) 6.80-7.20 (m, 24H), 7.35-7.48 (m, 12H), 7.50-7.65 (m, 4H). <sup>31</sup>P-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 360 MHz) 112.78. <sup>13</sup>C-NMR (CD<sub>2</sub>Cl<sub>2</sub>, 360 MHz) 124-150 (m). [α]<sub>D</sub><sup>20</sup> = 114.7 (c, 0.38, CHCl<sub>3</sub>). MS: 203 (100), 387 (65), 439 (48), 807 (50). HRMS C<sub>56</sub>H<sub>41</sub>O<sub>2</sub>P<sub>2</sub> 807.2566 Cal.: 807.2582.

20

### EXAMPLE 4

25

#### General Procedure for Catalytic Asymmetric Hydrogenation of Enamides

In a glove box, the Rh-phosphine complex was made *in situ* by mixing Rh(COD)<sub>2</sub>PF<sub>6</sub> (3.7 mg, 0.008 mmol) and a chiral phosphine ligand (0.8 ml of 10 mg/mL ligand in toluene, 0.012 mmol) in 19.2 ml of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was

30

stirred for 30 min. Then 2.5 ml of this solution was transferred to a 10 ml vial with an enamide substrate (0.1 mmol).

The hydrogenation was performed at room temperature under 20 psi of hydrogen pressure for 24 h. The hydrogen was released carefully and the reaction mixture was passed through a silica gel plug eluted with EtOAc. The enantiomeric excess was measured by GC or HPLC using a chiral GC or HPLC column without further purification. The absolute configuration of products was determined by comparing the sign of optical rotation with the reported data.

## **EXAMPLE 5**

### **Results of Asymmetric Hydrogenation of Enamides**

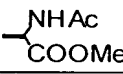
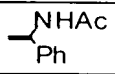
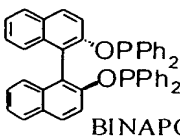
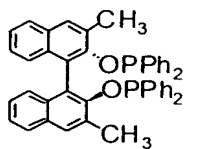
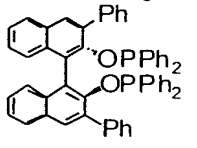
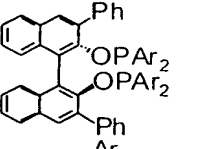
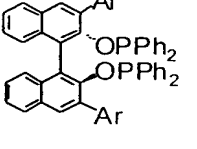
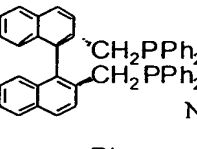
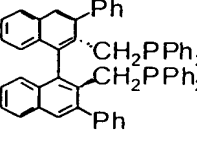
To examine the effectiveness of new chiral ligands, hydrogenation of a typical dehydroamino acid derivative and an enamide was carried out. The results are summarized in Table 1. The 3,3'-disubstituted bisphosphinite ligands (**11a-d**) are more effective than BINAPO (**3**) for asymmetric hydrogenation.

In the similar way, the 3,3'-disubstituted bisphosphine **15** is a better ligand for Rh-catalyzed asymmetric hydrogenation than NAPHOS (**6**).

We conclude that introduction of 3,3' substituted groups can restrict the rotation of phenyl groups adjacent to phosphines and therefore a well-defined chiral pocket around the transition metal is formed. The conformational rigidity is crucial for achieving high enantioselectivity for a number of asymmetric reactions.



Table 1. Rh(I)-catalyzed asymmetric hydrogenation

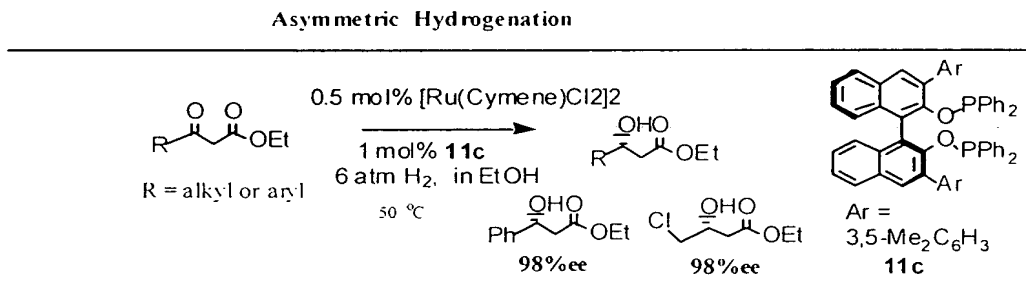
Ligand	Substrate	
		
entry 1  BINAP <b>3</b>	73% ee	28% ee
entry 2  <b>11a</b>	95 % ee	67% ee
entry 3  <b>11b</b>	>99 % ee	94% ee
entry 4  <b>11c</b>	95% ee	89% ee
entry 5  <b>11d</b>	93% ee	90% ee
entry 6  NAPHS <b>6</b>	54% ee	—
entry 7  <b>15</b>	99% ee	82% ee

The reaction was carried out at rt under 3atm of H<sub>2</sub> for 12 h in 3ml of THF with complete conversion (S/C = 100). Ar = 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

## EXAMPLE 6

### Asymmetric Hydrogenation of Beta-keto Esters

5           A number of beta-ketoesters can be reduced in high ee's using a Ru-3,3'substituted BINAPO (**11d**) compound as the catalysts. Particularly, the R group is aryl, heteroaryl, substituted aryl, alkyl and substituted alkyl species. These reactions can be carried out at low pressure and low temperature, which shows advantages over the reaction carried out with Ru-BINAP complex (90 atm,  
10   90 °C).



## EXAMPLE 7

15

### Asymmetric Synthesis of Beta-Amino Acids

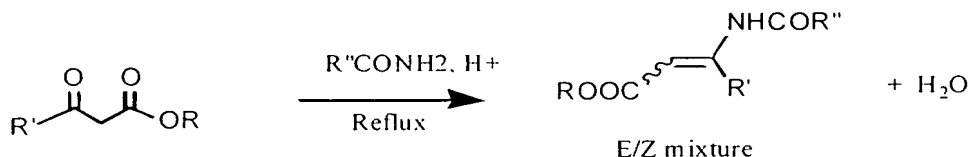
#### Synthesis of Starting Material 3-Acetamido-3-Aryl-2-Propenoates and 3-Acetamido-3-hetero-Aryl-2-Propenoates

20

Typical procedure: The starting material methyl 3-acetamido-3-phenyl-2-propenoate can be conveniently synthesized from cheap acetophenone in three steps according to known literature procedure in good yields. The literatures are Zhu, G.; Zhen, Z.; Zhang, X. *J. Org. Chem.* **1999**, 64, 6907-6910; Krapcho, A. P.;  
25   Diamanti, J. *Org. Synth.* **1973**, 5, 198-201. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 360 MHz) δ (Z

isomer) 2.17 (s, 3H), 3.77 (s, 3H), 5.29 (s, 1H), 7.37-7.45 (m, 5H); (E isomer) 2.38 (s, 3H), 3.77 (s, 3H), 6.65 (s, 1H), 7.37-7.45 (m, 5H).

#### An Effective New Way to Make Enamides



R', R'' = alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl

R = alkyl, aryl

5

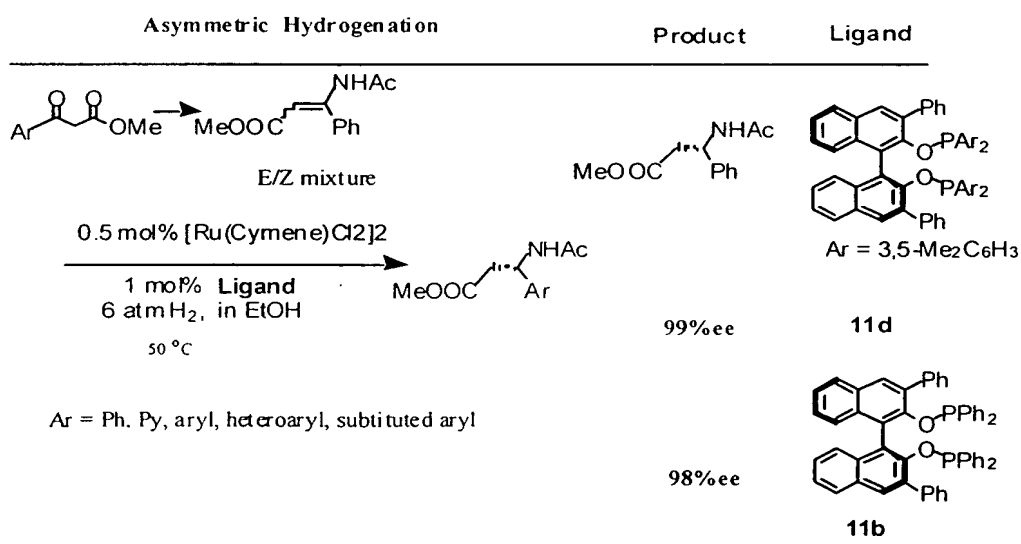
Alternatively, 3-acetamido-3-aryl-2-propenoates and 3-Acetamido-3-hetero-aryl-2-propenoates can be prepared through a new route by reacting acetamide with the corresponding beta-keto esters. A related example is demonstrated by Tschaen et al. *J. Org. Chem.* 1995, 60, 4324. The typical procedure involves addition of the corresponding beta keto-ester, an acetamide or other amide such as enamide, Amberlyst 15 or other acid catalysts in toluene. The mixture was heated at reflux for some hours with removal of water using a Dean-Stark trap. The end product was obtained after evaporating the solvent.

#### 15 Asymmetric Hydrogenation of methyl 3-acetamido-3-phenyl-2-propenoate

A dry Schlenk tube is charged with [Ru(cymene)Cl<sub>2</sub>]<sub>2</sub> (1.53 mg, FW = 612, 0.0025 mmol), chiral ligand 3,3'-diphenyl-xylyl BINAPO (**11d**, 4.82 mg, FW = 918, 0.0053 mmol), and then is evacuated and filled with argon. DMF (must be degassed by freeze-thaw cycles) (1 ml) is introduced under stream of argon. The solution is stirred at 100 °C for 10 min under argon, giving a clear reddish brown solution. The reaction mixture is cooled and concentrated at 1 mmHg at 50 °C with vigorous stirring and then at 0.1 mmHg for 1 h to give a reddish brown solid, which is used as hydrogenation catalyst.

25

To a solution of above catalyst in EtOH/DCM (4 ml, 3/1) in a glove box was added substrate methyl 3-acetamido-3-phenyl-2-propenoate (109 mg, 0.5 mmol). The hydrogenation was performed at 50 °C under 78 psi of hydrogen for 15 hours (not be optimized). The bomb was then cooled to room temperature and hydrogen carefully released. The solvent was removed and the residue dissolved in ether. The ether solution was washed with water and brine and dried over sodium sulfate. The ether solution was passed through a short silica gel column and concentrated to dryness to give pure products methyl 3-acetamido-3-phenyl-2-propanoate (known compound, see: Zhu, G.; Zhen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907-6910 (Rh/Duphos and BICP, 65% ee); Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543 (Ru/BINAP, poor ee)). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 360 MHz) δ 1.92 (s, 3H), 2.76-2.83 (m, 2H), 3.53 (s, 3H), 5.34 (m, 1H), 6.65 (br, 1H), 7.18-7.27 (m, 5H). Chiral GC Condition: Chiral Select-1000 column (dimensions 15m X 0.25 mm (i.d.)). Carrier gas: He (1 ml/min), 180 °C, isothermal; (S) t<sub>1</sub> = 11.68 min; (R) t<sub>2</sub> = 12.04 min.



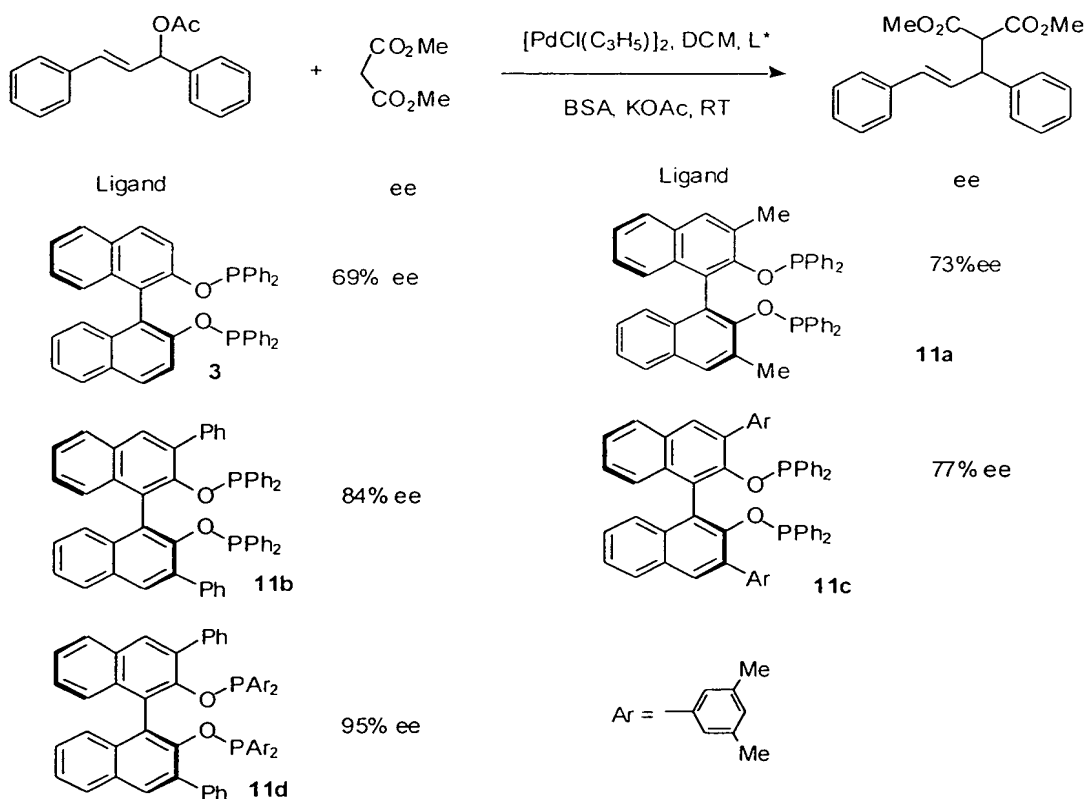
## EXAMPLE 8

### Asymmetric Allylic Alkylation

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Using 3,3'-disubstituted BINAPO as ligands, the Pd-catalyzed asymmetric allylic alkylation can be carried out and some results are listed below:

#### Pd-Catalyzed asymmetric allylic substitution



Ee values are determined by chiral HPLC (OJ Column H/IPA = 95/5)

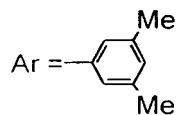
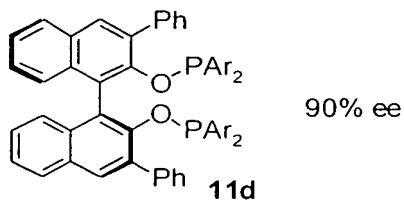
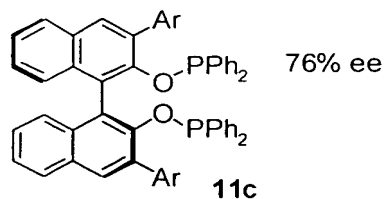
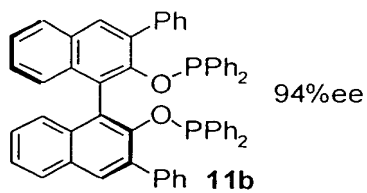
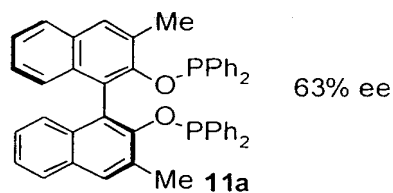
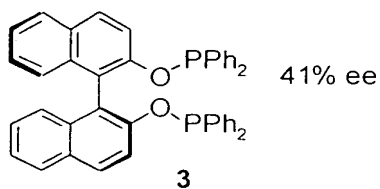
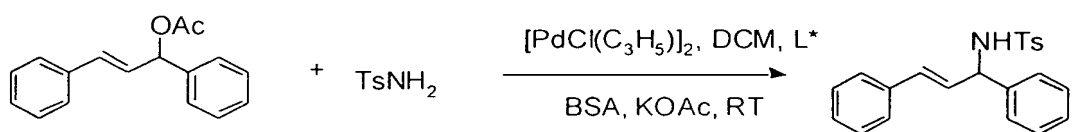
10

## EXAMPLE 9

### Asymmetric Allylic Alkylation with nitrogen nucleophile

- 5 Using 3,3'-disubstituted BINAPO as ligands, Pd-catalyzed asymmetric allylic alkylation with nitrogen nucleophiles can be carried out and some results are listed below:

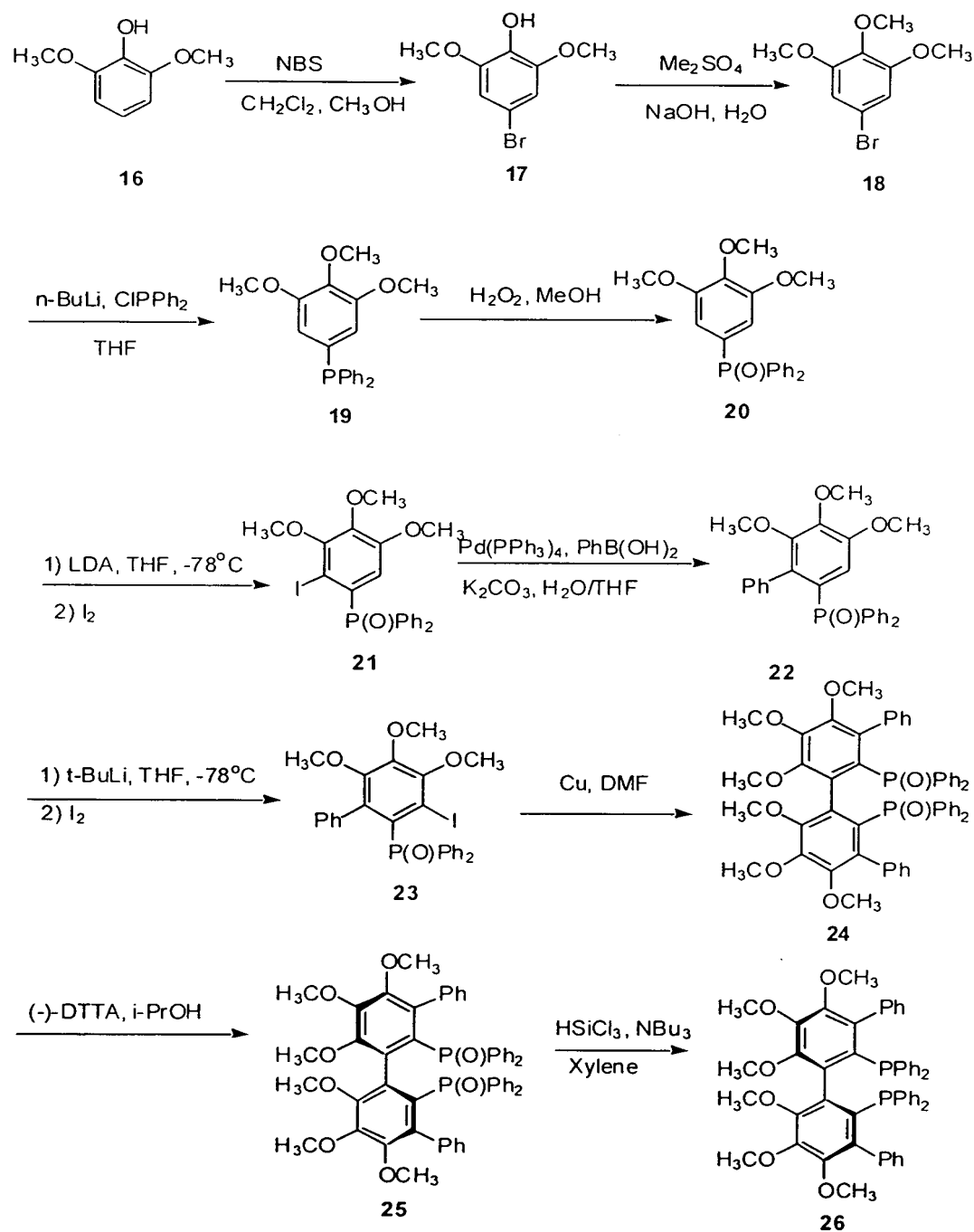
Pd-Catalyzed asymmetric allylic substitution



Ee values are determined by chiral HPLC (OJ Column H/IPA = 85/15)

### EXAMPLE 10

#### Synthesis of 3,3'-disubstituted biaryl phosphines(-)-(3,3'-diphenyl-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine)



### Synthesis of 4-bromo-2, 6-dimethoxy-phenol **17**

To a 2 liter flask equipped with a magnetic stirrer, thermometer, and  
5 nitrogen inlet, was added 77g (0.5 mol) of pyrogallol 1, 3-dimethyl ether, 5.8 ml  
of MeOH, and 750ml of CH<sub>2</sub>Cl<sub>2</sub>. To this solution was added 126mg (5mmol) of  
NaH (95%). The solution was stirred while cooling to -45°C with a dry-ice  
acetone bath. 94g (0.53mol) of powdered N-bromosuccinimide was added rapidly.  
The reaction mixture was then stirred for 1 hour at -35°C, heated to room  
10 temperature over next 30min, and finally refluxed for 30min. The CH<sub>2</sub>Cl<sub>2</sub> was  
removed under reduced pressure and the residue solidified. The tan solid was  
broken up and stirred well with 1 liter of ether. This was filtered and the residue  
was washed well with ether. The ether was evaporated under reduced pressure to  
yield a tan solid. The solid was placed in a 5 liter flask with 3 liters of ligroin (bp:  
15 90-110°C) and heated with stirring to 80°C. The hot solution was decanted from  
the brown oil and the hot yellow solution was allowed to cool at room temperature  
for 3hr. The white needles was filtered off and dried to yield 74g (63%) of **17**.

Ref: *J. Org. Chem.* Vol. 50, **1985**, 1099.

20

### Synthesis of 3,4, 5-trimethoxybromobenzene **18**

A mixture of 74g (0.32mol) of 4-bromo-2, 6-dimethoxy-phenol **17** and  
32g (0.8mol) of NaOH in 850ml of H<sub>2</sub>O was cooled to 10°C and 45ml  
25 (0.48mmol) of dimethyl sulfate was added. The mixture was refluxed for 3h and  
an equal amount of dimethyl sulfate (total 0.96mol) was then added. The mixture  
was refluxed for another 3h. Upon cooling overnight, the gray product solidified  
and was filtered off and dissolved in 1.2 l of ether. The ether solution was filtered  
to remove insoluble impurity and washed sequentially with 5% NaOH solution  
30 (200ml), water (2 X 200mL), and brine (200mL). The ether phase was dried over



Na<sub>2</sub>SO<sub>4</sub> to give a off-white solid, which was recrystallized in hexane (300ml) to give 62.3g (79%) of **18**.

#### **Synthesis of (3, 4, 5-trimethoxyphenyl)diphenylphosphine 19**

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To a solution of 3,4,5-trimethoxybromobenzene **18** (62.3g, 0.25mol) in dry THF (200ml) was added BuLi solution (169ml, 1.6M in hexane, 0.27mol) dropwise at -78°C within 45min. The resulting beige-colored suspension was stirred for an additional 1h at -78°C. Then PPh<sub>2</sub>Cl (61g, 0.277mol, 49.7ml) was  
10 added dropwise. The addition was complete within 2h. The resulting yellow solution was allowed to warm to 0°C within 2h and quenched by addition of NH<sub>4</sub>Cl solution (200ml). The organic layer was separated, washed with brine (250ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated. The solid was recrystallized from methanol to give 69.5g(80%) of **19**.

15

Ref.: *Helvetica Chimica Acta* Vol. 74, **1991**, 370-389

#### **Synthesis of 3, 4, 5-trimethoxyphenyl)diphenylphosphine oxide 20**

To a suspension of **19** (69.5g, 0.2mmol) in MeOH (500 ml) was added dropwise 30% H<sub>2</sub>O<sub>2</sub> (24.5g, 0.215mol) at 0°C. The resulting clear solution was stirred at ambient temperature for 1h. Then it was treated with sat. Na<sub>2</sub>SO<sub>3</sub> solution (75 ml) and 1N HCl solution (50 ml). The mixture was concentrated under reduced pressure to remove the MeOH. The solid residue was dissolved in  
20 CH<sub>2</sub>Cl<sub>2</sub> (300ml), washed with water (2x200 ml) and brine (200 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. To the resulting white solid was added 300ml hexane and the resulting suspension was stirred vigorously at room temperature. Filtration of the white solid powder gave 67.2g (0.182mol, 91%) of pure **20**.

30 Ref: *Helvetica Chimica Acta* Vol. 74, **1991**, 370-389

### Synthesis of (2-iodo-3,4,5-trimethoxyphenyl)diphenylphosphine oxide 21

To a solution of (i-Pr)<sub>2</sub>NH (31.88ml, 23.02g, 0.227mol) in dry THF (200ml) was added n-BuLi solution (125ml, 1.6M in hexane, 0.2mol) dropwise at  
5    -78°C. The addition was complete within 15min. After stirred at 0°C for 10min, the LDA solution was re-cooled to -78°C. It was then added via cannula to a flask containing a solution of **20** (67.2g, 0.182mol) in dry THF (200ml) over 20min. During the addition, the mixture was turned reddish-brown, and eventually a beige suspension was formed. After the reaction mixture was stirred  
10    for an additional 15min at -78°C, a solution of I<sub>2</sub> (50.6g, 0.2mol) in THF (200ml) was added dropwise. The addition was complete in 3h. A reddish-brown viscous paste was formed at the end of the addition. Then, the cooling bath was removed, and the mixture was allowed to warm to 0°C to form a clear red solution. The mixture was quenched by the addition of a Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (12g in 100ml H<sub>2</sub>O).  
15    The solution was concentrated to remove THF. The residue was dissolved in 300ml of CH<sub>2</sub>Cl<sub>2</sub>, washed with water (2 x 200 ml) and brine (200ml), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The brown paste was recrystallized in EtOAc (100ml) to give 55g (62%) of **21**.

20    Ref: *Helvetica Chimica Acta* Vol. 74, 1991, 370-389

### Synthesis of (2-phenyl-3,4,5-trimethoxyphenyl)diphenylphosphine oxide 22

To a 2 liter Schlenk flask was added (2-iodo-3,4,5-trimethoxyphenyl)  
25    diphenylphosphine oxide **21** (30g, 61mmol), phenylboronic acid (11.1g, 91mmol), and degassed THF (800ml). A solution of degassed saturated K<sub>2</sub>CO<sub>3</sub> (400ml) was added afterwards. The whole mixture was degassed with nitrogen for an additional 10min. Then, Pd(PPh<sub>3</sub>)<sub>4</sub> (1.22mmol, 1.4g) was added in the solution through one portion. The mixture was stirred at reflux under nitrogen for 24hrs.  
30    In situ <sup>31</sup>P NMR showed that the reaction was complete. The reaction mixture was concentrated under reduced pressure to remove THF and 400ml of CH<sub>2</sub>Cl<sub>2</sub> was

then added. The CH<sub>2</sub>Cl<sub>2</sub> layer was washed with water (200ml) and brine (200ml), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The solid residue was recrystallized from EtOAc (100ml) to give off-white product **22** (23g). The mother liquid was passed through a silica gel column to give another 4g of product **22**. The total yield was 98%.

**Synthesis of (2-iodo-6-phenyl-3,4,5-trimethoxyphenyl)diphenylphosphine oxide 23**

To a solution of (2-phenyl-3,4,5-trimethoxyphenyl)diphenylphosphine oxide **22** (26.5g, 59.7mmol) in dry THF (500ml) was added t-BuLi (47.7ml, 1.5M in pentane, 71.6mmol) dropwise at -90°C. The addition was complete within 2hrs. The solution was allowed to warm to -78°C and stirred for an additional 3h. Then a solution of I<sub>2</sub> in THF (100ml) was added dropwise at this temperature. The addition was complete in 2h. The resulting dark solution was allowed to warm to room temperature and stirred overnight. A solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (12g in 100ml H<sub>2</sub>O) was added. The resulting yellow solution was concentrated under reduced pressure. To the residue was added 500ml of CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was washed with water (100ml) and brine (100ml), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was recrystallized from EtOAc (100ml) to give a pure brown solid **23** (24g). The mother liquid was passed through a silica gel column to give another 5g of product. The total yield is 85%.

**Synthesis of (RS)-(3,3'-diphenyl-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) 24**

A mixture of (2-iodo-6-phenyl-3,4,5-trimethoxyphenyl)diphenylphosphine oxide **23** (7.4g, 12.6mmol), Cu powder (252mmol, 16g, activated by I<sub>2</sub> treatment), and DMF (200ml) was stirred at 155°C for 1hr. The cold mixture was evaporated to dryness at the rotor evaporator at 70°C. The residue was treated for a few min with CH<sub>2</sub>Cl<sub>2</sub> (200ml). The solid was removed by filtration and washed with

CH<sub>2</sub>Cl<sub>2</sub> (200ml). The combined filtrate was washed with sat. NH<sub>4</sub>Cl solution (2 X 100mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was crystallized from EtOAc (100ml) to give 5g (90%) of white product **24**.

5 **Resolution of (3,3'-diphenyl-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) 25**

To a mixture of (RS)-(3,3'-diphenyl-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) **24** (2.3g, 2.5mmol) and (-)-DTTA (-  
10 0.966g, 2.5mmol) was added 40ml of i-PrOH. The resulting slurry was heated to reflux to get a clear solution. Then it was cooled slowly to room temperature and stirred overnight. The salt of (-)-**25** and (-)-DTTA was obtained as white powder through filtration( ee: 95%). The salt was recrystallized one more time from 25ml i-PrOH and 1.1g of solid was obtained. The solid was dissolved in 50ml of  
15 CH<sub>2</sub>Cl<sub>2</sub>, washed with 3N NaOH (2x 50ml) and water (3x 50mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The solid (97.7%, 0.86g) was recrystallized from acetone to give enantiomerically pure product **25** (0.69g, 60%, ee>99.5%).

20 **Synthesis of (-)-(3,3'-diphenyl-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine) 26.**

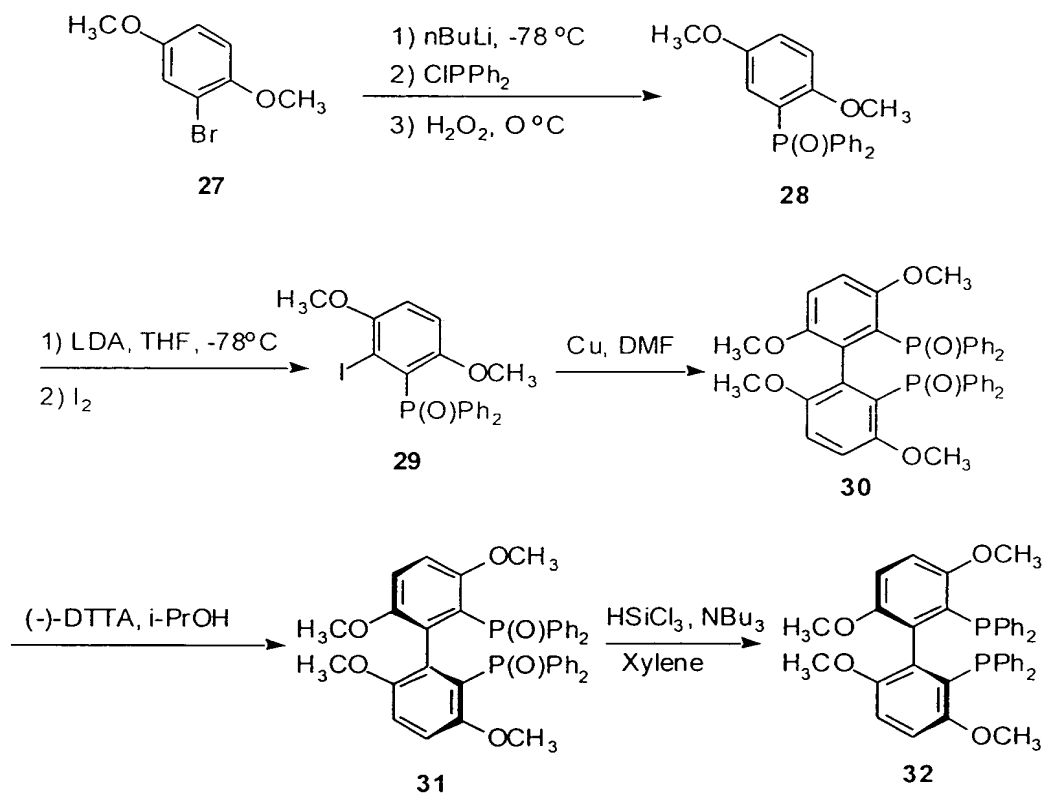
To a solution of (-)-(3,3'-diphenyl-4,4',5,5',6,6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) **25** (700mg, 0.79mmol, resolved from (-)-DTTA), tributylamine (6.5ml, 27.3mmol), and xylene (100 ml) was added HSiCl<sub>3</sub>  
25 (1.72 ml, 17mmol) dropwise at 0°C. The reaction was stirred at reflux for 2days. Some precipitates came out during the course. After cooled down, the reaction mixture was quenched with 30% degassed NaOH solution (20ml) in an ice-water bath. The resulting solution was kept at 60°C for 1h. The organic phase was transferred into another Schlenk flask through cannula. The water phase was re-  
30 washed with CH<sub>2</sub>Cl<sub>2</sub> (30ml\*2). The combined organic phase was washed with water (50 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. The

resulting yellow residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and passed through a basic Al<sub>2</sub>O<sub>3</sub> column to give a pure white solid **26** (400 mg, 59%).

### EXAMPLE 11

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#### Synthesis of 2,2'-(diphenylphosphanyl)-3, 6, 3',6'-tetramethoxybiphenyl



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#### (2,5-Dimethoxyphenyl)diphenylphosphine oxide

At -78 °C, 2.5M n-BuLi in hexane (48mL, 0.12mol) was slowly added to a solution of 1-Bromo-2,5-dimethoxybenzene (**27**, 25g, 0.115mol) in THF (250mL) causing the solution to become dark yellow (solid suspension). The reaction mixture was stirred at this temp for about 30 minutes, following by addition of

15

diphenylchlorophosphine (21.5 ml, 0.12 mol). During the addition, control the temp below  $-50^{\circ}\text{C}$  (add slowly). The resulting yellow solution was allowed to warm up to room temp (take about two hours). The saturated  $\text{NH}_4\text{Cl}$  solution (200 ml) was added and reaction mixture form two layers. The organic layer was washed with brine ( $2 \times 100\text{mL}$ ) and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed under vacuum to give a white solid.

Add MeOH (200mL) to the resulting white solid to form suspension. At  $0^{\circ}\text{C}$ , 33%  $\text{H}_2\text{O}_2$  (14ml, 0.13mol) was slowly added to above MeOH suspension.

The addition process takes about 20 minutes and the solid vanished promptly after all  $\text{H}_2\text{O}_2$  was added. The mixture was allowed to stir for one hour at  $0^{\circ}\text{C}$ , follow by adding saturated  $\text{NaHSO}_3$  solution (15ml) and stir for 30 minutes (the KI-Starch paper was applied here to make sure all peroxide was reduced). The solvent was removed under vacuum to give a white solid. The resulting solid was dissolved in  $\text{CH}_2\text{Cl}_2$  (200mL) and was washed with water (150mL) and brine (150mL), dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was also removed under vacuum to give a white solid. The crude product was treated with hot hexane ( $2 \times 100\text{mL}$ ) (to remove trace amount of impurity) to give pure product (**28**, 37.3g, 95.8%).

### **(3,6-Dimethoxy-2-iodophenyl)diphenylphosphine oxide**

A solution of LDA (6mmol) 1.5M in pentane was slowly added to the phosphine oxide (**28**, 1.69g, 5mmol) in THF (60mL) at  $100^{\circ}\text{C}$ . The resulting dark yellow solution (solid suspension) was allowed to warm up to  $-78^{\circ}\text{C}$  (take 30 minutes) and then stirred 3.5 hours at this temp. during which time the white solid precipitated. Solid  $\text{I}_2$  (1.78g, 7mmol) was added against a counter flow of  $\text{N}_2$  to the anion in THF at  $-78^{\circ}\text{C}$ . The reaction was allowed to come to  $0^{\circ}\text{C}$  and quenched with  $\text{Na}_2\text{S}_2\text{O}_3$  aq. solution (10mL). The solvent was removed under vacuum and the residue was extracted with  $\text{CH}_2\text{Cl}_2$  (50mL), washed with water (50mL), brine (50ml) and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed and the brown oil residue was treated with EtOAc (10mL) (to wash out most of the color

impurities, the product form white solid in EtOAc). Then the vacuum filtration gives the white solid (**29**, 1.0g, 43%)

#### **2,2'-(Diphenylphosphinoyl)3,3',6,6'-tetramethoxybiphenyl**

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Copper powder (320mg, 5mmol) was added to a solution of the iodide (**29**, 116mg, 0.25mmol) in DMF (10mL) and the reaction mixture heated to reflux for 8 hours. During the reflux, white solid formed along the wall of flask. The mixture was treated under vacuum to remove most of the solvent (before it cooled). The residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (20mL) and washed with water (2×10mL), brine (10mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed under vacuum and the resulting solid was washed with EtOAc (2mL) to give a white solid (**30**, 70mg, 83%).

#### **Resolution of 2,2'-(diphenylphosphinoyl)3,3',6,6'-tetramethoxybiphenyl**

15 (-) DTTA (0.579g, 1.5mmol) was added to diphosphine oxide (**30**, 0.674g, 1mmol) in EtOH (29mL) solution(at this time, DTTA can not dissolve in EtOH solution). The reaction mixture was heated up to reflux until all solid suspension was completely dissolved (take about 20 minutes). The resulting solution was allowed to stir overnight until crystal formed. The mixture was filtrated under vacuum and washed with cold EtOH (5mL). The resulting solid (0.405g, 75.1%) was added to CH<sub>2</sub>Cl<sub>2</sub> (20mL) and NaOH (20mL, 10% aq.) solution for about 5 minutes, and the entire insoluble solid disappeared. The organic layer was washed with water (2×10mL), brine (10mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed under vacuum to give a white solid (**31**, 99.3% ee).

#### **2,2'-Diphenylphosphanyl-3,6,3',6'-tetramethoxybiphenyl**

30 HSiCl<sub>3</sub> (542mg, 0.4mL) and NBU<sub>3</sub> (1.48g, 1.9mL) were added to diphosphine oxide (**31**, 70mg, 0.1mmol) in xylene (5mL) solution under N<sub>2</sub>

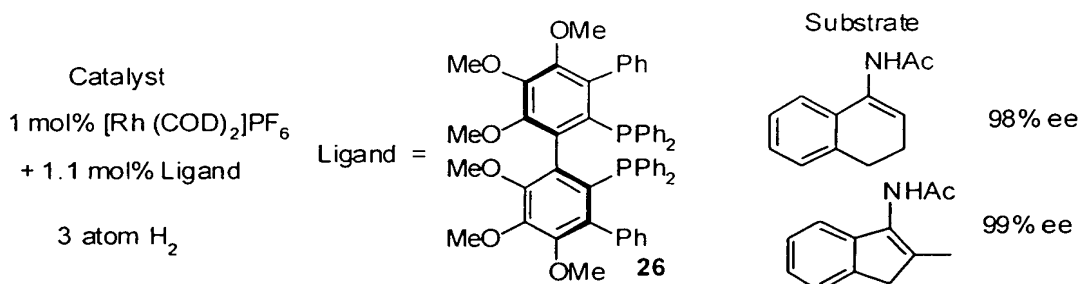
atmosphere. The reaction mixture was heated to reflux for 3 hours. The mixture was allowed to cool down to room temp. Then the degassed NaOH aq. solution (10%, 5mL) was added to reaction mixture at 0°C and stir for one hour. The organic layer was washed with degassed water (2×10mL), NH<sub>4</sub>Cl aq. solution (10mL), brine (10mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed under vacuum to give a pale yellow solid. After a short plug (silica gel, elute with CH<sub>2</sub>Cl<sub>2</sub>:Hexane=1:1), the solvent was evaporated under vacuum to give a white solid (still not pure white, a little bit pale yellow color) (**32**, 50mg, 75%).

## EXAMPLE 12

### Asymmetric Hydrogenation of Enamides Facilitated by Rh-Complexes with (-) (3, 3'-diphenyl-4,4',5,5', 6, 6'-hexamethoxybiphenyl-2,2'-diyl)bis-(diphenylphosphine) (**26**)

Rh-complexes with (-) (3, 3'-diphenyl-4,4',5,5', 6, 6'-hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine) (**26**) are good catalysts for hydrogenation of enamides. Introduction of 3, 3' substituted groups have some effects on enantioselectivity of asymmetric hydrogenation of enamides. Cyclic enamides can be hydrogenated with good enantioselectivity.

### Rh-Catalyzed Asymmetric Hydrogenation





The present invention has been described with particular reference to the preferred embodiments. It should be understood that the foregoing descriptions and examples are only illustrative of the invention. Various alternatives and  
5 modifications thereof can be devised by those skilled in the art without departing from the spirit and scope of the present invention. Accordingly, the present invention is intended to embrace all such alternatives, modifications, and variations that fall within the scope of the appended claims.